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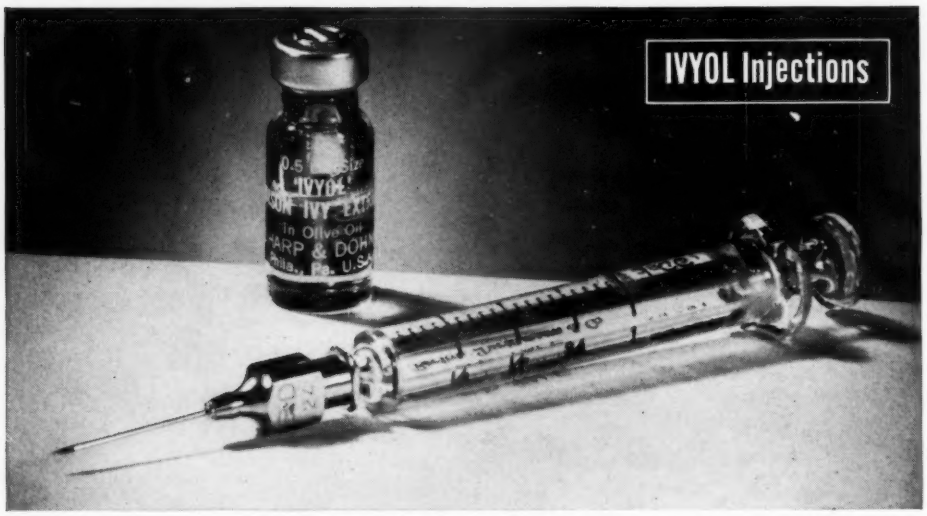

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The Bleeding Nipple

JOHN W. CLINE* AND PHILIP R. WESTDAHL

STANFORD UNIVERSITY SCHOOL OF MEDICINE, SAN FRANCISCO

There is wide divergence of opinion concerning the significance of discharge from the otherwise intact nipple. This is especially true of bloody discharge. The importance and causes of this symptom are discussed and a plan of investigation and treatment is presented. The methods outlined have proved satisfactory in clinical practice.

THERE is divergence of opinion concerning the significance of sanguineous discharge from the otherwise normal nipple. Some authors have found the incidence of malignancy associated with this symptom to be high and others believe it to be low. It has been said that bleeding from the nipple always arises from benign papillomata but every sizeable series includes instances of carcinoma and in some the incidence is about 50 per cent.

Certain reasons for these differences of opinion are apparent. Few hospitals maintain cross index filing systems for symptoms. Clinical histories may omit such a striking and important manifestation. Certain patients ignore bleeding and do not seek medical attention. It is probable that a considerable number of cases presenting this symptom as a result of a benign lesion do not come to light in statistical studies. The predominant importance of carcinoma also would tend to weight the figures in favor of an association between malignancy and bleeding.

The same breast is not infrequently the site of multiple lesions at the same time. Small papillomata easily escape gross detection and may be overlooked in routine pathologic examination. Even with most meticulous search they may be difficult to find and yet may be the source of bleeding. If such occur in a breast which also presents carcinoma the conclusion may be reached that the carcinoma is responsible for bleeding when in reality it is not.

Bleeding from the nipple is usually intermittent and variable intervals occur between episodes. Some of these may be quite long. Carefully elicited histories reveal instances of transient bleeding in the past with no recurrence for years thereafter. It is likely that the incidence is considerably higher than the recorded cases show, but it is not a common symptom. Public education campaigns of recent years have made patients more aware of the importance of abnormal discharge of any type, and the frequency with which they present themselves with this as the sole or the principal symptom is increasing.

CAUSES

Numerous pathologic conditions have been cited as sources of bleeding. Many of these are clinical curiosities. The common causes are

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Presented at the thirty-fifth annual Assembly of the Interstate Postgraduate Medical Association, Chicago, 1950.

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papilloma, adenocystoma and carcinoma. There is general agreement that, except for rare conditions, bleeding is due to an intraductal epithelial neoplasm or one communicating with the duct system.

Intraductal papilloma—This is the most common source of bloody discharge. The majority of these are situated in the larger ducts underlying or near the areola. Most are composed of delicate epithelial filaments with a central vascular core. They arise from the duct wall and float free in the larger ducts in the early stages. They follow the course of least resistance as they increase in size and therefore grow along the duct. Intraductal papillomata usually are single but may give the appearance of lesions with multiple points of origin due to involvement of communicating ducts and secondary attachment to the wall at other sites in the course of growth. They may be multiple and may be widely distributed throughout the breast in the condition referred to as intraductal papillomatosis.

THE delicate strands are easily injured and minor, unnoticed trauma will initiate bleeding. When this occurs blood will distend the duct and present at the nipple.

Bleeding usually is intermittent and dependent upon repeated trauma. The vascular core may be injured and atrophy; fibrosis or even calcification may occur.

This type of lesion produces practically all instances of bleeding in the absence of a palpable tumor and accounts for a high (but we believe still undetermined) percentage of all instances of bleeding.

The papilloma may be sessile from the outset, less subject to injury and, therefore, less apt to bleed. Papillomata are often present without bleeding and may cause serous discharge. Some achieve large size and are easily palpable.

Cystadenoma—This condition is called by a variety of names, which fact results in confusion. It presumably begins as a papilloma in one of the smaller ducts which in the process of growth distends the duct and grows into numerous communicating ducts. It acquires many attachments to the walls and appears to have many sites of origin. It tends to lie peripheral to the areola and may be near the margin of the breast.

Due to the type of tumor, its location in the smaller ducts, and its less frequent communication with the nipple, it is less likely to produce bleeding or other types of discharge. It is more frequently a silent tumor which has some of the gross characteristics of an infiltrating growth. Bleeding, however, does occur and may be frequent or continuous.

This lesion is often erroneously diagnosed microscopically as carcinoma and may be partially responsible for the relatively high reported incidence of bleeding associated with malignancy.

Intracystic papilloma—Many cysts are devoid of epithelial lining but such may be present and papillomata do occur in cysts. These are a relatively rare source of bleeding because cysts usually do not communicate with the duct system and are considered by some to arise as a result of blocked ducts. In the instances of intermittent communication with the larger ducts cyst fluid and blood may appear at the nipple. At the outset intracystic papillomata may resemble the more centrally situated intraductal type. They are fragile but they are protected from trauma and even if they bleed the blood is apt to be confined to the cyst. As they grow they may fill the cyst. Some are flat, sessile growths and these are believed to be more apt to undergo malignant degeneration.

Carcinoma—As pointed out earlier, there is difference of opinion concerning the frequency

with which bleeding arises from carcinoma. Except in early papillary carcinoma, bleeding is rarely, if ever, associated with carcinoma in the absence of a palpable tumor.

If one subscribes to the opinion of Stewart that most carcinoma of the breast originates from duct epithelium, he must recognize that such may communicate with the ducts and produce bleeding at any stage of development.

In our experience the association between bleeding and carcinoma is not common, and accounts for a relatively small fraction of the total cases of bleeding. Nonetheless, bleeding from carcinoma does occur and its importance cannot be minimized.

Benign precancerous lesions—There is no uniformity of opinion as to what constitutes a precancerous lesion of the breast. Bloodgood, Bartlett and others consider benign papillomata, especially of the adenocystic type, to be precancerous lesions. Stewart and others minimize their importance in this role. Stewart observes that the term "precancerous" usually is applied to lesions in which the microscopic picture is suggestive but not necessarily conclusive of malignancy.

He further believes that the fact that one sees malignancy arising in an otherwise benign lesion does not establish a causal relationship. He describes the female breast as a precancerous organ and states that the most common precancerous lesion of the breast is carcinoma of the other breast.

Breast sections exhibit widely varying pictures of epithelial proliferation and growth potential. One may not lightly dismiss papilloma as not being a precancerous lesion, even though groups of patients who have bled from the nipple have been followed carefully for years without operation and have presented a low incidence of carcinoma. While the figures are low, in most series they represent a higher incidence of cancer than in the general female population in the same age brackets.

DIAGNOSIS

Discharge from the nipple, with the exception of galactorrhea, is important and requires investigation. It is probable that bloody discharge is more significant than other types and must be differentiated from the pseudosanguineous exudate of a greenish or brownish color which may be mistaken for old blood.

Physical examination—The most important element of preoperative diagnosis is careful palpation of the breast. If a tumor is found and pressure over the tumor causes blood to be extruded from the nipple the source of bleeding is obvious.

If no tumor can be palpated the breast should be compressed progressively in concentric circles beginning at the periphery and the nipple observed for the appearance of discharge at each point of pressure. In the absence of a mass the usual cause is a centrally situated papilloma and blood may not be expressed until the region of the areola is reached. The duct orifice from which it appears should be identified and it should be observed whether this corresponds to the portion of the breast submitted to pressure.

A cord-like thickening may be felt or suspected at the site of an enlarged or distended duct. Moistening the fingers with ordinary lubricating jelly aids in palpating structures which are difficult to feel.

Transillumination—This method of examination has been disparaged but is occasionally of value in demonstrating a papilloma or a blood-filled duct. If a collection of blood is present, a fusiform opaque shadow may be seen or a narrow opaque band may be made out running radially from the region of the nipple.

Stained smears—Smears of the discharge stained by the Papanicolaou method or other methods may add important information. The presence or absence of blood cells can be determined. Examination of epithelial cells may yield clues to the diagnosis, but as yet the information gained by this method seldom, if ever, establishes the nature of the disease with sufficient certainty that one may predicate treatment upon it. Biopsy or excisional biopsy is necessary for this purpose. The one exception is when an unlocalized source or multiple sources of bleeding are present and the smears show unmistakable tumor cells with or without malignant characteristics.

Certain authors have believed that they could establish a definite diagnosis of a breast lesion by smears of discharge, but we agree with the majority who consider this conclusion open to serious question. The method is becoming more accurate with increasing experience and knowledge but at the present time still must be viewed only as an additional aid to diagnosis.

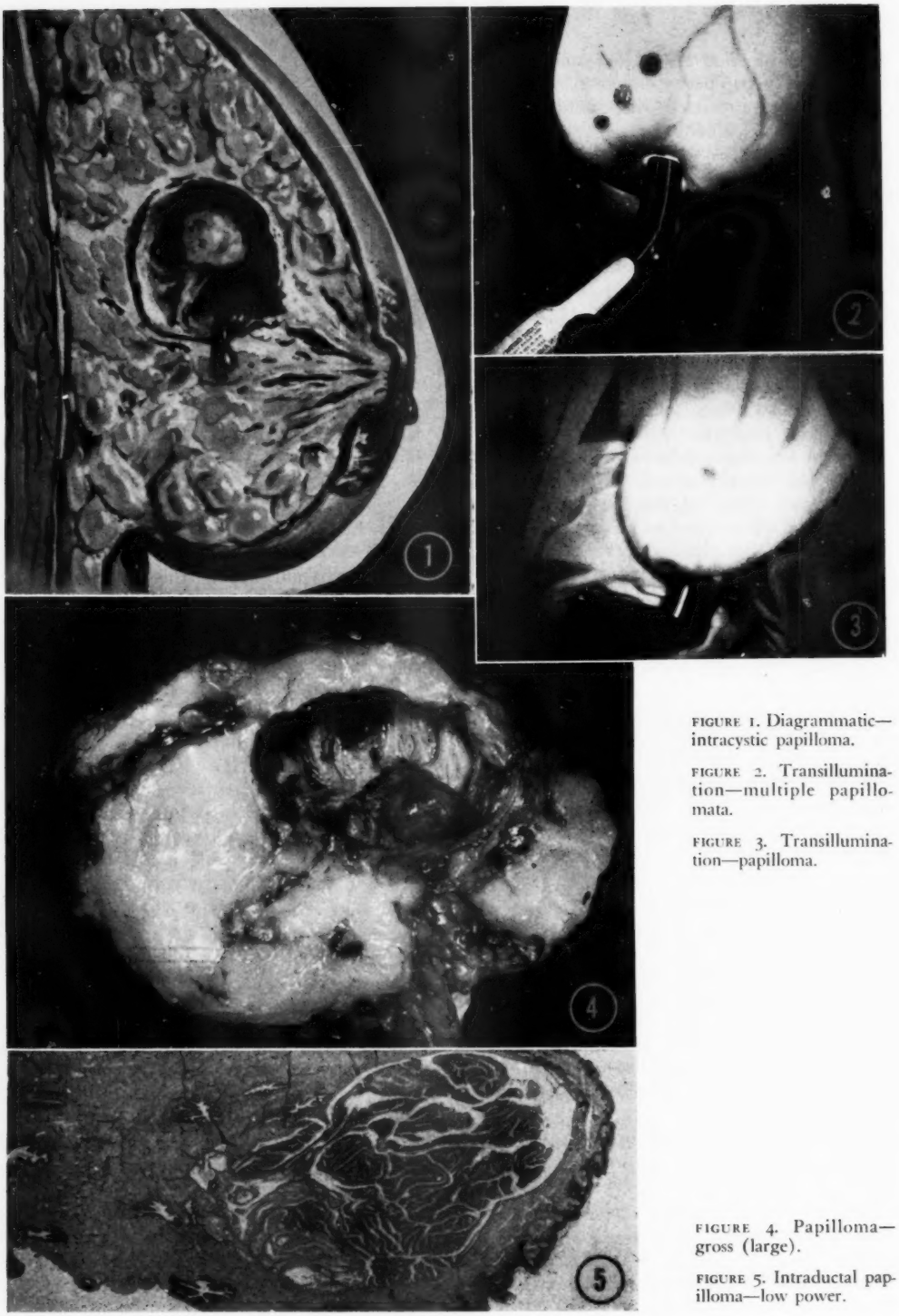

FIGURE 1. Diagrammatic—intracystic papilloma.

FIGURE 2. Transillumination—multiple papillomata.

FIGURE 3. Transillumination—papilloma.

FIGURE 4. Papilloma—gross (large).

FIGURE 5. Intraductal papilloma—low power.

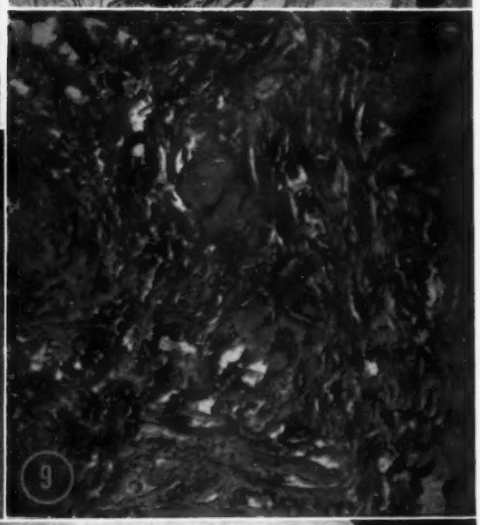

FIGURE 6. Multiple papillomata adenosis, chronic cystic mastitis.

FIGURE 7. Papillary cystadenoma (single).

FIGURE 8. O. G. Cross section, duct, papilloma.

FIGURE 9. O. G. Carcinoma, malignant cells, heavy stroma.

FIGURE 10. Babcock's operation.

TREATMENT

The method of procedure following examination of the patient depends upon the findings.

Bleeding with a palpable tumor—A tumor of the breast of itself requires treatment. When associated with bleeding the course to be followed should be the same unless the discharge can be demonstrated to arise from a site other than the tumor itself; in this event the tumor should be explored first. If it is malignant no other disease condition has clinical importance. If upon microscopic examination the tumor is found to be benign, the source of bleeding should be sought independently.

Gross characteristics usually reveal the nature of the tumor. Frozen sections should be made but the limitations of this method should be recognized. The percentage of error in doubtful cases is reasonably high; paraffin sections are much more accurate.

We as surgeons must rely upon and have confidence in our pathologists. If a positive diagnosis of malignancy is made, the radical operation should proceed at once.

If there is question as to the malignant nature of the lesion, final decision should await study of the permanent sections. Delay is undesirable but moderate delay has not been definitely demonstrated to be harmful and is preferable to unwarranted radical surgery. This is especially true in the younger age group.

Localized bleeding without palpable tumor—This arises in most instances from a centrally located papilloma. The procedure of Babcock is excellent for dealing with this situation. A circumareolar incision is made for half the circumference centering about the site of the duct from which blood can be expressed. The enlarged bluish duct usually can be seen. A needle previously inserted through the duct orifice makes its identification and dissection easier.

We prefer to add a radial incision extending along the course of the duct and to perform a segmental resection of the breast. The duct and the surrounding breast tissue are carefully examined for undetected pathology. If none of importance is found and if the microscopic sections are not certainly positive for malignancy, the wound is closed.

Non-localized bleeding—If the site of bleeding cannot be determined or if bleeding apparently comes from multiple sources, one faces the dilemma whether to observe the patient or to submit her to mastectomy. Smears of the discharge may be of value in making this decision.

If tumor cells with malignant characteristics are found, a simple or radical mastectomy is indicated depending upon the certainty of recognition of the cells as malignant. In the older age group simple mastectomy may well be the procedure of choice when any type of tumor cell is present though malignancy is not certain. This later may prove to have been unnecessarily radical.

In younger women close, repeated and protracted observation is the preferred course. The hazard of malignancy is comparatively slight and if present it can be found and dealt with in an early stage. This procedure has little associated danger and is preferable to an unnecessarily mutilating operation.

In most instances either the bleeding will cease or can be localized during the period of observation, and treatment then may be based upon sounder considerations.

Particularly in younger women removal of a breast inflicts important psychologic trauma and should be done only when proper indications for the operation exist.

REFERENCES

1. Adair, F. E.: Sanguineous discharge from the nipple and its significance in reference to cancer of the breast. Ann. Surg. 91:197, 1930.
2. Babcock, W. W.: A simple operation for the discharging nipple. Surgery 4:914, 1938.
3. Bartlett, E. I.: Papilloma of the breast. West. J. Surg. 56:12, 1948.
4. Bloodgood, J. C.: Benign lesions of the female breast for which operation is not indicated. J.A.M.A. 78:859, 1922.
5. Bloodgood, J. C.: Borderline breast tumors. Ann. Surg. 93:235, 1931.
6. Campbell, O. J.: The bleeding nipple. Surgery 19:40, 1946.
7. Cheatle, G. L. and Cutler, Max: Tumors of the Breast. Philadelphia, J. B. Lippincott Company, 1932.
8. Copeland, M. M.: Newer aspects of benign tumors of the breast. Arch. Surg. 55:590, 1947.
9. Foote, F. W., Jr. and Stewart, F. W.: A histologic classification of carcinoma of the breast. Surgery 19:74, 1946.
10. Geschickter, C. F.: Diseases of the Breast. Philadelphia, J. B. Lippincott Company, 1945.
11. Gray, H. K. and Word, G. A.: Significance of mammary discharge in cases of papilloma of the breast. Arch. Surg. 42:203, 1941.
12. Haagensen, C. D., Stout, A. P. and Phillips, J. S.: Unpublished data.
13. Jackson, D. and Severance, A. O.: Cytological study of nipple secretions. Texas State J. Med. 41:512, 1946.
14. Macdonald, Ian: The bleeding nipple as a diagnostic and therapeutic problem. California Med. 68:1, 1948.
15. Oberhelman, H. A.: Benign lesions of the breast. S. Clin. North America 38:95 (February) 1948.
16. Slaughter, D. P. and Peterson, L. W.: Indications for simple mastectomy. Surg., Gynec. & Obst. 85:456, 1947.
17. Stewart, F. W.: Tumors of the breast. Army Institute of Pathology.
18. Wakeley, C.: Duct papilloma of the breast. Lancet 1:62, 1947.

Anorectal Examinations in General Practice

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Proctologic examination in general practice is essential to the practice of good medicine. The technical requisites of an unobstructed view of the anorectal canal to the 10 inch level are not beyond the scope of the general practitioner. The purpose of this presentation is to outline the simple steps necessary in such an examination. Illustrative case material is submitted, emphasizing the value of this standard and accepted procedure of diagnosis. The legal obligations of the practitioner of medicine in this respect are emphasized.

When I attended medical school one of my professors insisted that the first duty of a consultant was to make a rectal examination. No doubt a great many of you can recall experiences which verify this statement. Unfortunately at that time the consultant's rectal examination was limited to that of digital palpation, which I regret to say is still a more or less accepted procedure. Living as we are today in a so-called "cancer age," it is by becoming cancer-conscious and equipping ourselves not only with the facility but also with the necessary training that we can make a complete visual examination of the rectum and lower colon a part of the routine physical. In this way we as physicians can live down the old adage: "If you don't get your finger in the rectum, sooner or later you will get your foot in it." In other words, we can usually see the lesion even if it is early if we'll only look! It is hoped that through the presentation of this subject lesions which have heretofore been overlooked will be discovered before they result in serious infection or undergo malignant degeneration.

In his introductory remarks in Bacon's first volume on the "Diagnosis and Treatment of Diseases of the Anus, Rectum, and Sigmoid Colon," Babcock[1] states: "In a previous age the general practitioner often depended on a consulting specialist for even a digital examination of the rectum. Now he is expected to be fairly familiar with at least the simple diagnostic methods of proctology."

In the original text Bacon[2] writes: "It is the duty of the physician to make a complete and thorough examination. By some this may be considered disagreeable and embarrassing to the patient, yet there is no excuse for its omission. It is well to bear in mind that existing pathology is overlooked through carelessness or failure of examination more frequently than through lack of knowledge of the anorectal and colonic regions."

Buie[3] has gone on record that in 90 per cent of cases where some disease process is present in the terminal bowel there are discoverable findings present on visual observation with the sigmoidoscope.

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Presented at the thirty-fifth annual Assembly of the Interstate Postgraduate Medical Association of North America, Chicago, 1950.

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In his plea for routine proctoscopy as part of a thorough physical examination, Nesselrod[4] insists that it is "a procedure which is essential to the practice of good medicine." He makes it very clear that by the use of this diagnostic procedure a double purpose is accomplished: first, the prevention of disease; second, the early diagnosis of cancer.

In a recent investigative review and clinical presentation, Scarborough[5] concluded that 1 in 20 adults harbors one or more adenomatous polyps in the terminal bowel. The significance of these findings is that cancer originates in benign adenomatous polyps. By the early discovery and removal of polypoid lesions, carcinoma is prevented. The accomplishment of this objective is obviously not to be reached without a routine visual examination with the sigmoidoscope and roentgenologic study of the colon lying beyond the reach of the examining instrument.

Viewing the entire problem from a completely different angle, Regan[6] concludes that "the practitioner's legal duty to a patient with neoplastic disease is no different than in any other case. When a physician undertakes to render professional services to any patient, he assumes certain legal obligations. He must possess the degree of skill and knowledge commonly possessed by other reputable physicians in the community; he must exercise care, diligence and judgment equal to that of other practitioners who engage in the treatment of similar cases; and he must keep abreast of progress in the profession, utilizing accepted and standard procedures in diagnosis and treatment."

TABLE 1

SERIES OF CASES WITH SYMPTOMS OF TERMINAL BOWEL DISEASE ILLUSTRATING RELATIVE INCIDENCE OF NEW GROWTHS

(Clinical Survey)

	TUMORS		MALIGNANT TUMORS
	Cases	Per cent of total	Per cent of total
Miscellaneous diagnoses	220		
Extrarectal growths	2		
Diverticulous granuloma	1		
Adenomas (polypoid)	35	11	2
Benign 27			
Malignant 7			
Precancerous (4-year) 1			
35			
Malignancy (anus, rectum, colon)	45	15	15
TOTALS	303	26	17

CLINICAL SURVEY

Two years ago the author reviewed 303 active case histories of patients who had presented themselves for colo-proctologic consultation, examination, and treatment (Table 1). Of this number 220 were listed as coming under the following diagnoses: abscess, fistula, fissure, hemorrhoids, pruritis ani, condylomas, prolapse, postinjectional slough, fecal impaction, factitial proctitis, chronic ulcerative colitis, diverticulitis and benign stricture. One individual had an obstruction of the bowel due to a diverticulous granuloma. Two patients presented tumor formation extrarectal in location. In 35 patients adenomatous polyps were discovered incidental to routine visual examination of the terminal bowel. In the remaining 45 patients malignancy involving the anus, rectum or colon was the lesion demanding consideration.

In 7 of the 35 individuals presenting visible adenomas incidental to routine examination, on tissue analysis there was evidence of malignancy existing at the time of excision. In one instance a precancerous polyp was removed in a 4 year old girl. In the remaining 45 of the 303

cases, malignant lesions involving the anus, rectum or colon were proved to exist. By way of passing comment in regard to this latter group of patients with malignancies, 4 of the 45 had been receiving injection treatment for hemorrhoids. One patient had had three injection treatments during the previous month. In a second instance the course of injection treatments covered a period of several months. A third patient had received two courses of injections from two different physicians, and in the last instance the injection program was considered ineffective because of persistent bleeding and the patient was subjected to surgical removal of the existing hemorrhoids.

CASE REPORTS

To emphasize the importance of an early complete examination in the diagnosis and treatment of rectal disease, the writer has thought best to review briefly these records, each of which teaches an important clinical lesson.

Case 1—E. H., 52 year old male executive, whose field of activity carried him frequently to Central America. His chief complaint was alteration in bowel habitus of 10 months' duration with recurring episodes of looseness. For a period of several months this was accompanied by intermittent hyperpyrexia, abdominal cramping and backache. Because of these symptoms he consulted a physician who specialized in tropical medicine. At this time, some five and one-half months prior to examination by the writer, stool examination proved to be positive for *Endamoeba histolytica*. During a period of several months' observation and treatment for amebiasis, two proctoscopic examinations were made by the attending physician. While away from home at a later date the patient was hospitalized in another city at which time he was subjected to further clinical study which included two proctoscopic examinations and a barium enema. Following this study the patient was referred to the writer for surgical treatment of an obstructive sigmoidal lesion. The x-ray films accompanying the patient disclosed a colon filled with barium except in the lower and midportions of a long sigmoid loop.

Examination revealed a well preserved male with a fixed irregular lower left abdominal mass extending well to the midline and half way to the umbilicus. With previous history of four proctoscopic examinations confirming variable degrees of ulceration without ruling out malignancy, it was considered advisable to sigmoidoscope this patient under anesthesia following adequate preparation. In the inverted position a proliferative annular stricture was observed beginning at the five and one-fourth inch level. A stricture which extended to an indefinite level was lined with an ulcerated necrotic membrane as visualized with the five-eighths inch sigmoidoscope only for a short distance. Two biopsies were taken from the growing edge for malignancy and a third sample was taken from the ulcerated surface for amebic investigation. Histologic examination disclosed an adenocarcinoma grade 3 plus. No amebae were observed.

Surgical exploration of the abdominal region revealed a large fixed mass draped over the pelvic brim, arising from the rectosigmoid and extending up to the midsigmoid colon. Localized extension involved two regional loops of small bowel, the great vessels and a portion of the upper sigmoid. A large solitary nodule extruded from the superior surface of the right lobe of the liver. A palliative colostomy was incorporated in the closure of the abdomen.

Comment—The lesson in this case is painfully obvious. The mistaken impression that the symptoms were referable to the lower bowel simply because the patient had traveled in the tropics was a fatal error, and tragically this error might have been avoided by an early visual inspection of the sigmoid.

Case 2—I. A., an office worker aged 56, a widow with two married daughters, gave the history of malignancy of large bowel on her mother's side of the family. Her chief complaint was a bloody discharge, bright red in color, streaking the stool and coloring the toilet water on several occasions of recent date.

In addition to interno-external hemorrhoids, a sigmoidoscopic examination disclosed the presence of an irregular, firm, slightly raised lesion, 1½ by 2 cm. in size, on the left posterior wall at the five inch level. Biopsy revealed this to be an adenocarcinoma grade 2.

Surgical treatment consisted of a two-team abdominoperineal proctosigmoidectomy with permanent abdominal colostomy. Pathologic study of the specimen removed revealed this small growth to have invaded the bowel wall with metastatic extension to an adjacent perirectal gland.

Comment—This history presents a happier side of the malignant picture. Early diagnosis and complete removal of a small lesion proved histologically to be maligant offer a fairly hopeful prognosis. At this date it is too early to be certain about a cure, but repeated examinations will be made to keep in contact with local development.

Case 3—N. D., 22 years of age, an expectant mother of seven months, observed a bloody discharge at the time of defecation. On investigation of the stool a piece of tissue was recovered and taken to her family physician. An examination of this tissue revealed the presence of malignancy with a classification of adenocarcinoma grade 2.

A sigmoidoscopic examination disclosed a pedicular stump 0.5 cm. in diameter and elevated 8 mm. above the surrounding mucosa. This was attached at the 3½ inch level in posterior midline. The tip of this polypoid residual tissue presented a raw eroded surface at the site of separation of the malignant polyp.

Surgical treatment consisted of a wide resection of the bowel wall surrounding the pedicle and its mucosal attachment. Pathologic study and comparison of slide from original biopsy disclosed no evidence of an extension of the growth into regional tissues.

Comment—In this case we may expect a hopeful outcome because an alert patient and a careful physician followed a suspicious clue. A small lesion was identified and widely resected. The absence of signs of malignancy in the pedicle is of course encouraging, but again we cannot be sure of a cure until a sufficient period of observation has passed.

Three case histories have been briefly reviewed. These individuals received careful study and consultation; diagnosis was established and treatment given. In the last two instances the value of being cancer-conscious in the presence of the first appearance of blood from the terminal bowel, plus early adequate examination, led to the diagnosis of early malignancy with prompt surgical attack. In the other case, delay on the patient's part to submit himself for examination long after a chain of symptoms was well established proved to be a fatal mistake, and the situation was not improved by prolonged treatment for amebic colitis without adequate endoscopic and roentgenologic study.

SYMPTOMS REFERABLE TO THE TERMINAL BOWEL

A COMPLETE history and physical examination must be routine. Intensive study of a rectal disorder should never obscure the possibility of disease elsewhere in the body. The symptoms elicited from the patient which refer to the terminal bowel are essentially related to those of colonic function and the act of defecation in physiologic sequence.

Alteration in bowel habitus, a cardinal symptom, may be either of functional or structural origin. Functional alteration in intestinal motility is more commonly of neurogenic etiology and varies with type and degree of sympathetic imbalance. Change of pathologic origin in bowel habitus deals with altered tissue states which may be of intrinsic or extrinsic origin and falls into one of two etiologic groups: (1) infectious origin or (2) other new growth. The size, shape, consistency and color of stool require correlation with this cardinal symptom. Likewise ease of evacuation and completeness of same together with protrusion or prolapse of tissue mass are related factors. "Colitis" has been a diagnostic term in common use for many years, usually being applied to any abnormal variation of intestinal motility of the large bowel, whether it be sluggish or hypermotile in degree. Gross negligence too frequently arises with respect to this cardinal symptom which is mistakenly considered of functional rather than of pathologic origin. This can be attributed to lack of adequate visual observation (endoscopic) and to depending solely on digital palpation, stool analysis for parasites and ova, and barium enema.

Bleeding, the second cardinal symptom, may arise from a lesion anywhere in the intestinal tract. Bloody discharge, dark in color, varying from black tarry consistency to that of "coffee grounds,"—as a rule unmixed with stool—indicates the source of origin to be in the upper intestinal tract. Occult blood, ascertained only by laboratory analysis, indicates a slowly progressive loss from an ulcerative lesion in the right colon. However, the appearance of fresh blood suggests the presence of bleeding in the lower colon, rectum or anus. It has been stated that 80 per cent of malignancy of the gastrointestinal tract with exception of the stomach can be visualized with the 10-inch sigmoidoscope. It is also a known fact that 50 per cent of patients developing malignancy in the terminal bowel are inoperable by the time the diagnosis is established. The symptom of bleeding has literally become a medical football by virtue of a patient-doctor incompatibility that exists today. In the first instance, the patient does not like to mention the appearance of blood as related to these parts of his or her anatomy. Secondly, the physician is inclined to follow the line of least resistance on ascertaining the history of bleeding after proving to himself there is no gross lesion elicited by digital palpation. He concludes that the patient has hemorrhoids and prescribes measures for their relief without completing an adequate visual examination of the parts.

Pain, still another of the cardinal symptoms of lower bowel disease, varies greatly in type and severity depending on the causative lesion and the segment of the terminal bowel from which it arises. A knowledge of the applied physiology of these parts helps one ascertain whether this symptom is of colonic, rectal or anal origin. For example, pain of a cramping character associated with alteration in bowel habitus indicates an obstructive or ulcerative lesion of the colon or rectum. Vague indefinite rectal pain not associated with bowel habitus suggests that the pain is of skeletal origin. On the other hand, acute anorectal pain which brings the patient promptly to the examining

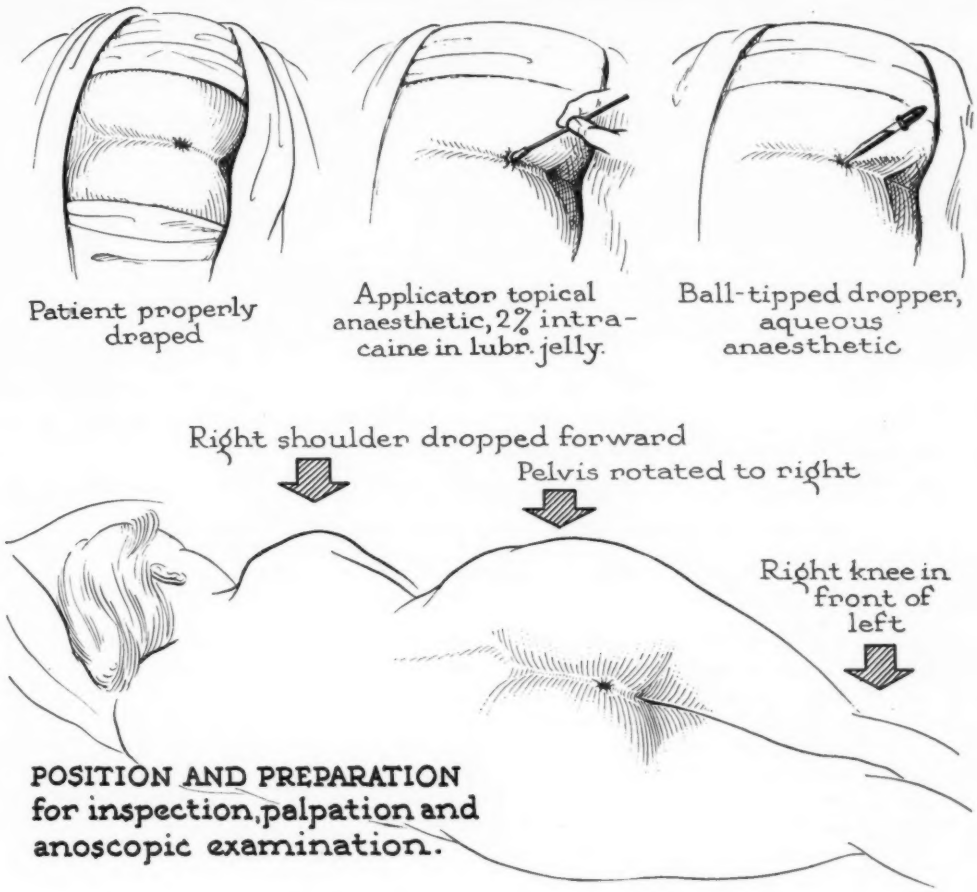
Patient properly draped
Applicator topical anaesthetic, 2% intracaine in lubr. jelly.
Ball-tipped dropper, aqueous anaesthetic
Right shoulder dropped forward
Pelvis rotated to right
Right knee in front of left
POSITION AND PREPARATION for inspection, palpation and anoscopic examination.

FIGURE 1. Position and preparation of patient for anorectal examination.

physician indicates an ulceration, infection or thrombosis of the vessels of the anorectal canal.

Swelling of long standing about the anal margin may be of a neoplastic nature. Acute progressive swelling with pain and at times a possible elevation of temperature indicates abscess formation, whereas the sudden formation of a focal swelling with stinging sensation and pain about the anal margin indicates hemorrhoidal thrombosis.

Discharge from the anus and anal margin when persistent and foul smelling may be associated with malignancy of contiguous tissues. Persistent soiling of the parts may accompany incontinence following anal surgery or perineal laceration, lymphopathia venereum, condylomas, fistulous disease, prolapsing hemorrhoids and pruritis ani.

Loss of weight, the sixth and last cardinal symptom, when of colo-proctologic origin, may accompany chronic infectious disease of the anorectal region. Chronic ulcerative colitis more or less fits into this category. Loss in weight associated with malignant disease of the terminal bowel indicates delay in diagnosis with not only probable localized extension of growth, but also metastasis to the liver.

EXAMINATION ROUTINE

The effective examination of the anus, rectum and lower sigmoid colon need not be a compli-

FIGURE 2. Technic of inspection of the perianal region.

cated procedure. This should consist of inspection, palpation and anoscopic observation in the right or left Sims' position, followed by sigmoidoscopic visual observation to the 10-inch level (25 cm.). Several types of examining tables are available which are a convenience but not a necessity. Necessary clothing having been loosened or removed, the patient is put in the left Sims' position and properly draped (Figure 1). The preliminary application of a topical anesthetic in a water-soluble lubricant to the anal canal and low mucosal surfaces will not only facilitate routine procedure but will also permit a fair study of the most painful lesions. This is best accomplished by the nursing attendant at the time of preparing the patient several minutes in advance of examination. The lower bowel surfaces are cleansed two hours prior to examination by use of saline enema until water returns clear.

Inspection of the anus, buttocks, sacral and perineal areas is facilitated by having the patient bear down, thus disclosing any existing abnormalities (Figure 2). Skin tags or external hemorrhoids, when present, are a deformity on the anal margin and are indicative of anal disease. Hypertrophied skin folds give evidence of existing pruritis ani. A condyloma is an infected hyperplasia of perianal skin. Fissure-in-ano or painful ulcer is commonly accompanied by an edematous skin fold or formation of a sentinel pile. Draining skin sinuses are indicative of a fistulous process which along with abscess formation results from an extension of an infection from the anal crypts, ducts and glands.[7] Pilonidal sinuses are the result of an embryonic rest of epithelial tissue. Sebaceous cysts when present cause little or no inconvenience. Epidermoid carcinoma is commonly overlooked in its early stage; it is manifested by an irregular hyperplasia of epithelium of the anus and anal canal.

Palpation (Figure 3) of the perianal tissues may elicit infiltrating or cord-like processes extending into the anal margin. Extreme sphincter spasm is indicative of anal disease and may be the result of a focus of infection in crypts, ducts and glands with resulting contracture and stenosis of the anal canal and consequent alteration of bowel habitus. Gentleness is a prerequisite in palpation and digital examination. Pain, spasm and stenosis call for the small finger to be used in palpation instead of the index finger.

Bidigital examination using the index finger and thumb aids in outlining the anus, anal canal and areas in question, and by comparison with corresponding areas of the opposite side small focal lesions may be identified. The well lubricated finger is approximated to the anus after palpating the perianal, perineal and sacral areas, making gentle pressure against the

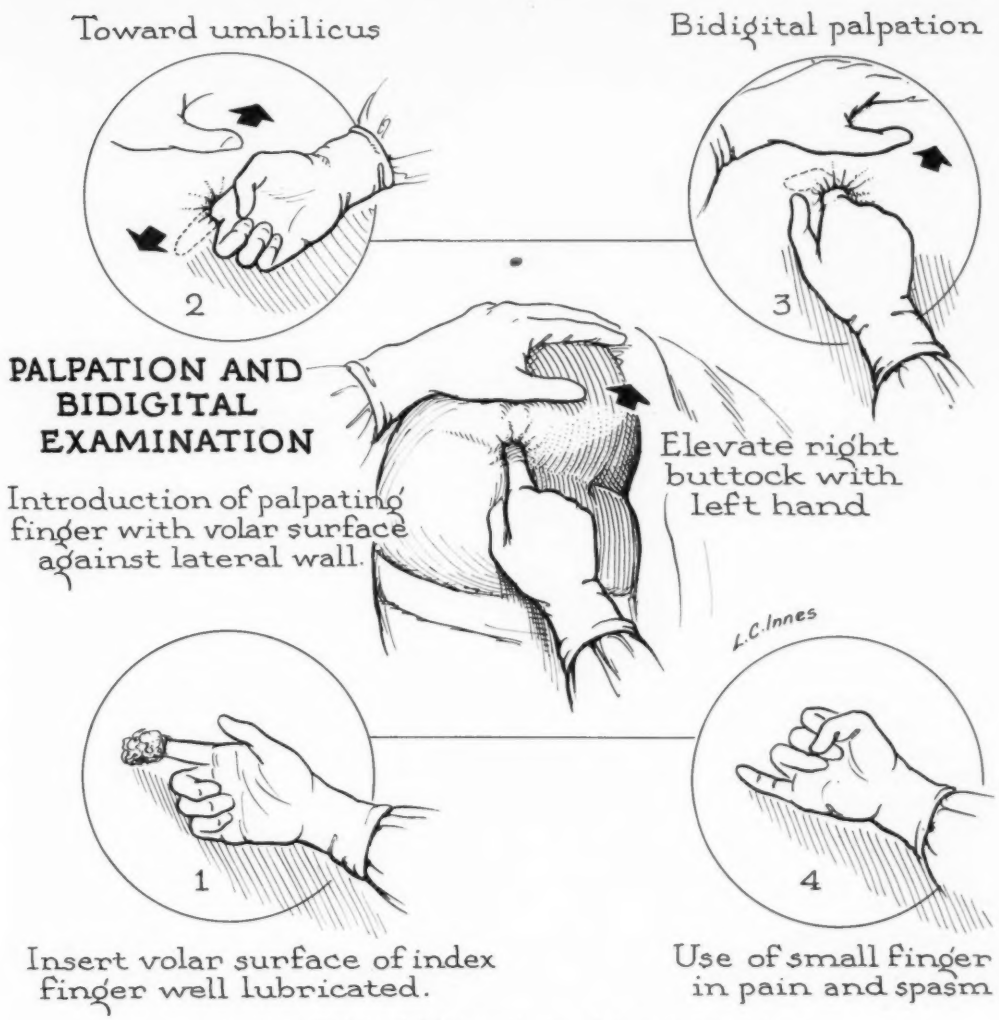

FIGURE 3. Technic of digital examination of the anorectal canal.

sphincter ring with the volar surface of the examining finger approximating the lateral wall of the anal canal. The finger is introduced downward and forward toward the umbilicus through the anal canal and sphincter ani. The lower Houston valves are reached by the palpating finger as well as seminal vesicles and prostate in the male subject and pelvic organs in the female. By having the patient bear down during palpation one may outline the rectosigmoid junction in many instances. Contrary to common opinion, hemorrhoidal varicosities are not discernible to the palpating finger unless thrombosed, infiltrated or hyperplastic.

Benign stricture can usually be identified as well as foreign bodies, fecal impactions, residual lesions following hemorrhoidal injection, abscess, thrombosis, ulcer depressions, stricture, polyps, adenomatous growths or adenopathy of perirectal glands of Gerota. Malignant stricture usually occurs in the rectosigmoid and sigmoid colon beyond finger length. Inguinal lymphatic drainage of perianal and perineal structures calls for palpating the bilateral inguinal node chain.

Anoscopic examination (Figure 4) under direct or indirect lighting is best accomplished by using an open end anoscope with a removable obturator. This instrument has the distinct advantage of an unobstructed view of the hemorrhoidal areas as well as of the crypt line. The well lubricated anoscope is introduced into the anal canal making gentle pressure with the beveled edge of the obturator against the lateral wall of the anal canal, directing the instrument forward toward the umbilicus through the sphincter ani. After removing the obturator, observation is made of the regional mucous membrane surfaces, crypt line and anal canal. This is best accomplished by having the patient strain and bear down as in the defecatory act as each area is observed. Thus can be noted the presence of hypertrophied anal papillae, polypoid formation and the degree of varicosity. It is obvious that under these circumstances the degree of anorectal redundancy and prolapse of rectal mucosa is readily discernible.

Localized gland, duct and crypt infection is verified under visual observation by expressing purulent exudate from the crypt orifice with the margin of the anoscope. Likewise the primary opening of a fistula may be detected and in many instances confirmed by gentle probing. Fissure formation is observed more commonly in the posterior commissure and may be accompanied by an edematous hypertrophy of an anal papilla on its upper margin as well as a sentinel pile at the ano-cutaneous line.

Sigmoidoscopic examination (Figure 5) can be carried out in several positions besides the lateral or Sims' position. The inverted position facilitates the passing of the lighted examining instrument beyond the rectal ampulla into the pelvic colon. The knee-shoulder position accomplishes this same purpose in the cooperative patient. By using ordinary household or hospital facilities, the patient may be jackknifed over the edge of the bed or ordinary table with elbows and head supported on a pillow on the floor or low stool.

Preparation of the patient calls for a saline enema one to two hours prior to examination. "Topesthesia" is preliminary routine as previously described, together with the passage of the well lubricated gloved finger to put the muscles at ease and to determine muscle resistance. A 10-inch, distally lighted sigmoidoscope is used which is five-eighths of an inch in diameter (or just the size of a dime) on its distal or working end. The well lubricated sigmoidoscope is passed and carried downward and forward toward the umbilicus. When the instrument is through the sphincter ring, the obturator is removed and further passage of the instrument is carried on under direct vision. Suction is helpful in removing any retained liquid content whereas swabbing readily cleans the soiled surfaces. The application of a saturated solution of magnesium sulfate helps relax muscle spasm. Withdrawal of the scope a short distance obviates an apparent blind pouch in the lower sigmoid, permitting a straightening out of the figure "S" formation and further passage to the 10-inch level. Mild inflation allows visualization one or more inches beyond the end of the instrument.

Every square inch of the mucosal pattern should be observed and this is best accomplished on withdrawal of the instrument under mild inflation. Diverticulous openings with possible contained fecaliths may be observed; if so, it is well to evaluate the degree of inflammatory reaction of the tissues associated with the disease process.

Pressure with the distal end of the examining scope irons out the Houston valves permitting observation of both the upper and under surfaces. Oblique flexion of the hand holding the instrument permits complete study of the sacral curve. By having the patient strain while in the inverted position any increased excursion of the sigmoid, rectosigmoid and rectum is observed. At this time it is possible to note the presence of a hidden rectal prolapse, an infrequent cause of incomplete and delayed evacuation and a condition more commonly overlooked in infancy and childhood.[8]

One occasionally sees discoloration of mucous membrane characteristic of a melanosis coli. Any alteration in the mucosal pattern should be noted and a descriptive record made of the lesion and its exact anatomic location. This is imperative in dealing with polypoid lesions because of their precancerous nature which requires exacting treatment consideration as well as future periodic observation.

Biopsy of a cancerous growth as well as of all adenomatous polyps under treatment is in order. Sigmoidoscopic examination and record of findings should precede and supplement roentgenologic study of the colon; likewise x-ray

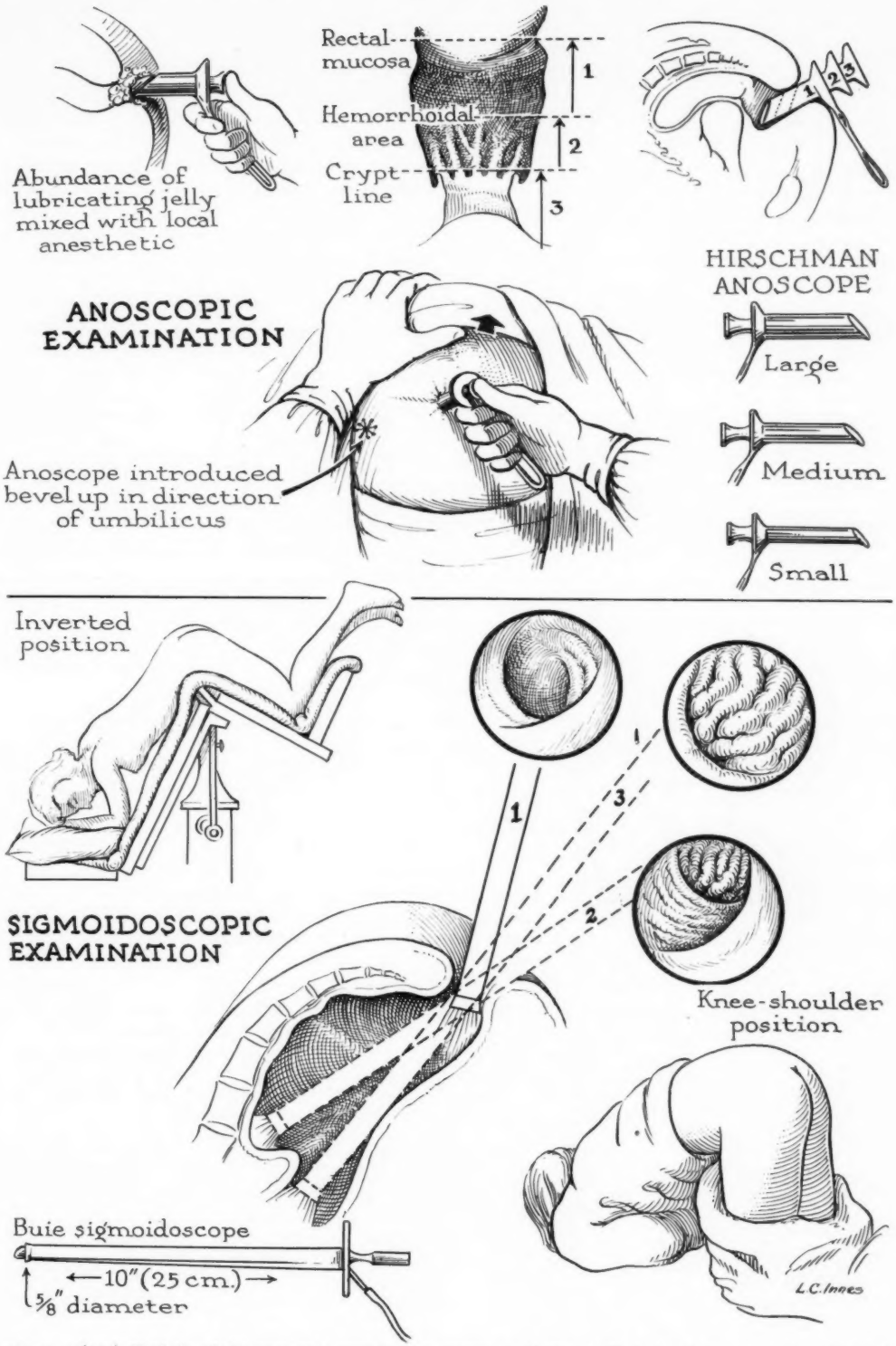

FIGURE 4 *(top)*. Technic of the anoscopic examination. FIGURE 5 *(bottom)*. Technic of the proctosigmoidoscopic examination.

examination and findings should be a supplement to every examination of the terminal bowel in which the history or findings are questionable. An incomplete or inadequate examination of the terminal bowel calls for a repeat sigmoidoscopic examination under anesthesia.

CONCLUSIONS

Routine anorectal examination as part of a general physical examination merits the consideration not only of the general practitioner but also of the internist and surgeon. The accomplishment of an unobstructed view of the anorectal canal to the 10-inch level will not only give the physician the satisfaction of doing thorough work, but will also serve as a measure to detect the presence of early malignant lesions. The technical requisites of the routine examinations are not beyond the scope of a general practitioner. It has been the purpose of this presentation to outline the simple steps necessary in such an examination. When these procedures have been learned and constantly used, the physician will come to recognize the worth of the old adage that "an ounce of prevention is worth a pound of cure."

REFERENCES

1. Babcock, W. W.: Introduction in Bacon, H. E.: Diagnosis and Treatment of Diseases of the Anus, Rectum and Sigmoid Colon. Philadelphia, J. B. Lippincott Company, 1938.
2. Bacon, H. E.: Anus, Rectum and Sigmoid Colon. Philadelphia, J. P. Lippincott Company, 1938, p. 48.
3. Buie, L. A.: Practical Proctology. Philadelphia, W. B. Saunders Company, 1937, p. 43.
4. Nesselrod, J. P.: Proctology in General Practice. Philadelphia, W. B. Saunders Company, 1950, p. 54.
5. Scarborough, R. A. and Klein, R. R.: Polypoid lesions of the colon and rectum. Am. J. Surg. 76:723-727 (December) 1948.
6. Regan, L. A.: Legal responsibility of the general practitioner in neoplastic disease. California Med. 68:102 (February) 1948.
7. Hill, M. R., Shryock, E. H. and Rebell, F. G.: Role of the anal glands in the pathogenesis of anorectal disease. J.A.M.A. 121:742-746 (March) 1943.
8. Hill, M. R. in Litchfield and Dembo: Therapeutics of Infancy and Childhood. Philadelphia, F. A. Davis Company, 1942, Vol. 2, pp. 1330-1336.

THE GREEKS HAD A WORD FOR IT

"I AROUSE TO ACTIVITY," the phrase represented by the Greek word in this month's cover painting, could as well typify Claude Bernard (1813-78) as the hormonal structures released by the various glands of the endocrine system. Though perhaps better known for his studies on digestion, Bernard also first proposed the doctrine of internal secretions of certain ductless glands. This famous French physiologist proved that, in addition to secreting bile, the liver also produced sugar and this function was independent of sugar in the diet. With his discovery, Bernard initiated the development of modern endocrinologic research and the identification of the hormones which are becoming ever more prominent in the study and treatment of disease.

Apprenticed to a local pharmacist when still a boy, Bernard found the work dull and spent what time he could spare writing poetry and drama. When he was 21, he left for Paris and after completing his training there, served as an assistant to Magendie, then leading physiologist of France. Bernard's first work on digestion led to the experimental studies which showed that digestion was not completed in the stomach but was continued in the intestine through the action of the pancreatic secretion.

Following his discovery of production of glycogen by the liver, Bernard went on to fundamental studies of vasomotor physiology. In 1854, the Sorbonne established a special Chair of Physiology for him and, in 1865, he published his classic book, "Introduction to the Study of Experimental Medicine."

Reprints of Edmund Kopietz' cover, mounted and ready for framing, are available on request to *Postgraduate Medicine*, 516 Essex Building, Minneapolis 3, Minnesota. Price: $1.00.

Complications of the Third Stage of Labor

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This paper includes management of the third stage of labor which should end with a critical period one hour after the delivery of the placenta. Placental delivery should exclude a radical, forcible and manual expression as a general policy, except in hemorrhage, and should be replaced by watchful waiting. Complications discussed are: postpartum hemorrhage, bleeding from cervical and vaginal lacerations, retained placental remnants, retention of placenta or retained placenta, placenta accreta, inversion of the uterus and retraction ring.

Any discussion of the third stage of labor and its complications or abnormalities would not be complete without some discussion of normal management of the third stage of labor. The third stage begins after the birth of the baby and ends with delivery of the placenta. In addition, it should be emphasized that there is a critical period of one hour or so after delivery of the placenta in which the patient should not be neglected and this period becomes an integral part of the discussion of the third stage of labor although by definition it is not included.

The management of the third stage of labor through a century of progress in obstetrics to the present time has evolved from a radical, forcible and manual expression of the placenta to a policy which is ordinarily one of watchful waiting—the exception, severe bleeding—until the placenta is separated. This is in contrast to the earlier methods of traction on the cord and manual removal, the latter attendant with the very grave dangers of infection and excessive bleeding.

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Presented at the thirty-fifth annual Assembly of the Interstate Postgraduate Medical Association, Chicago, 1950.

These procedures were followed by the Credé method which aimed at the hastening of placental separation and expressing the placenta from the uterine body as soon as the baby was born. In the Credé method strenuous kneading was performed, in an effort to stimulate and contract down the uterus with ultimate separation of the placenta. Finally the hand was applied to the abdomen so that the thumb and fingers were placed on the anterior and posterior surfaces of the uterus, respectively, and during a contraction, firm and steady pressure was made in the axis of the inlet. The procedure is compared to pitting a cherry. Of course, this method displaced the earlier methods of traction on the cord and manual removal, undoubtedly saving lives by the avoidance of infection and hemorrhage.

It is a fact from the foregoing statements and experience that any attempt to deliver the placenta before it is separated from the uterus—hemorrhage the main exception—is more or less useless and hazardous, leading to such complications as hemorrhage, placental remnants, inversion of the uterus and infection.

My own treatment of the third stage of labor

is specifically as follows: After the baby is born, I simply hold my abdominal hand on the fundus noting its consistency and position. Initially the uterus tends to rise in the abdomen and takes a position somewhat to the right. As long as it contracts well with no tendency to bleed, I neither knead nor compress it. I wait for the signs of placental separation. These signs are as follows:

1. Elevation of the uterus due to placental separation and the passage of the organ downward into the lower uterine segment and vagina. The placenta, in this position, tends to push the uterus upward.
2. The uterus, originally discoid in shape, maintains a permanent globular shape in relaxation when the placenta separates.
3. Advancement and protrusion of the umbilical cord.
4. Sudden gush of blood.
5. Distinct wave felt in the cord in an unseparated placenta, known as Pinard's sign.
6. Wrinkling and roughening of the uterus at the area of separation which is known as the DeLee sign.

If these signs of separation are present, then I expel the placenta. I see no advantage in delaying the expression of the placenta if it is separated from the uterus and in the lower uterine segment and vagina.

My own method of placental expression is a combination of the Calkins and Pastore methods. With my abdominal hand, I place my thumb on the anterior uterine surface and my fingers on the posterior uterine surface, with the other hand above the symphysis pubis, thereby preventing the uterus from entering the pelvis and eliminating the employment of the uterus as a piston according to Pastore. It is obvious that with my thumb and fingers a compression expulsion and downward thrust is accomplished.

COMPLICATIONS OR ABNORMALITIES OF THE THIRD STAGE OF LABOR

Postpartum hemorrhage—Bleeding may occur during the third stage of labor, immediately following the third stage or during both periods. Postpartum hemorrhage is defined as bleeding in access of 500 cc. during the first 24 hours after delivery. The incidence is 10 per cent. It is an important fact that patients who bleed around 600 cc. or more will have an incidence of 25 per cent puerperal sepsis.

Immediate causes of postpartum hemorrhage are as follows: uterine atony, which occurs in 90 per cent of the cases; cervical and vaginal lacerations, which occur in about 5 per cent of the cases; retention of placental remnants—uncommon cause of early postpartum hemorrhage, but frequently a cause of late or of puerperal bleeding.

Other causes which may be classified as uncontrollable and controllable causes are:

Uncontrollable—a large baby, multiple pregnancies, hydramnios, premature separation of the placenta and placenta previa.

Controllable—operative deliveries, anesthesia, lacerations, prolonged labor, exhaustion of the mother and mismanagement of the third stage of labor. It has been proved that the minimizing of operative deliveries in obstetrics definitely reduces the incidence of postpartum hemorrhage. Postpartum hemorrhage is commonly seen in version and extraction and difficult forceps operations. Ether anesthesia is more apt to be followed by hemorrhage than some of the other anesthesias. There is a significant increase in postpartum hemorrhage in prolonged and exhaustive labors. In addition, in prolonged labor with maternal exhaustion, the uterus is a part of the general fatigue and the combination of exhaustion, hemorrhage and infection may spell death for the patient.

The clinical picture of postpartum hemorrhage may be a deceiving one, easily misinterpreted and its treacherous features may be poorly adjudged—with ultimate death.

The bleeding after placental delivery is not one of continuous, profuse hemorrhage but a seepage or trickling, drop by drop, going on over a period of considerable time but amounting to an astonishing blood loss with the situation becoming critical. Usually there is sufficient time for treatment before the situation becomes critical unless the blood loss is precipitous. The effect of blood loss may vary in patients according to their general physical condition—antecedent anemia, prolonged and exhaustive labor, etc. The signs of shock and hemorrhage are well established and need no elaboration; however, an admonition is that the slow, insidious bleeding may show initially little change in the pulse and blood pressure but the time finally arrives when the compensatory vascular mechanisms

are unable to accommodate themselves to further blood volume loss, with a sudden fall in blood pressure, elevation of pulse and death if the patient has not been properly evaluated and treated.

The diagnosis as to the source of the bleeding is certainly important from the standpoint of treatment. Frequently the blood loss is considered coming from the uterus and due to atony when actually it is due to cervical or vaginal lacerations. If the uterus is well contracted and the blood is bright red and continuous, the bleeding is probably due to cervical or vaginal lacerations. The characteristic appearance of dark, venous blood usually points to uterine cavity bleeding and is more apt to be associated with a uterus which is not well contracted or which tends to relax. It is true that both types of bleeding may occur following major obstetric operative deliveries. Personally, I inspect the vagina and cervix in all deliveries. It is a "must" in my practice and it should be a "must" in everyone's practice, particularly following operative deliveries.

Treatment of third stage bleeding—In any discussion of the treatment of third stage bleeding, it is important to point out that there is a certain amount of bleeding as a result of the transient separation of the placenta. It is good practice to give the patient 1 cc. of PITOCIN® (10 units) intramuscularly as soon as the baby is born; this procedure hastens placental separation, and I personally feel it reduces the amount of blood loss. If external hemorrhage is observed and the uterus is not firmly retracted and signs of placental separation are not present, the uterus should be massaged but not by a classical Credé procedure. If signs of placental separation are present then the placenta should be expelled according to the technic already mentioned. However, if the bleeding continues to be excessive and reaches a blood loss of 400 to 500 cc. with the placental signs of separation absent, then manual removal of the placenta must be considered.

I emphasize that a Credé method employed at this point (otherwise kneading and squeezing the uterus through the abdomen) as a rule often traumatizes both the placenta and the myometrium, adds insult to injury and aggravates the difficulties. Bleeding following the placental delivery is going to be in part dependent upon the immediate care after the placental expression. Good practice is to give 1/320 gr. of ERGOTRATE® intravenously immediately after the placental expression and, in addition, to massage the uterus.

On our obstetric service, we insist that a nurse stay with the patient for one hour after delivery and never leave the patient's bedside. She places her abdominal hand on the uterus noting its size and consistency and at intervals justifiably massages the uterus. She reports at once to the doctor on the service any excessive external bleeding for which she is diligently watching over the course of an hour. Additional ergotrate or pitocin may be administered if the bleeding is a little more than normal but not excessive. At this time judgment is paramount as to the determination of blood loss and the possible consideration of blood replacement.

If bleeding persists after the procedure just described and more active treatment is indicated, I recommend bimanual compression which massages the posterior surface of the uterus with the abdominal hand, the anterior uterine surface with the other fist, the latter being so applied that the knuckles rub against the anterior uterine wall. This procedure delivers abdominal massage, produces considerable uterine stimulation, compresses the venous sinuses and good contraction of the uterus is maintained on the vessels. I feel that more can be accomplished by this procedure than by the intrauterine pack.

At this stage when I would consider bimanual compression, some obstetricians would consider the intrauterine pack. I agree with Cosgrove in this aspect of treatment relative to the uterine pack and I quote: "At about this juncture most authorities advise packing the uterus; this I do not approve. It seems to me entirely unphysiologic. Up to this time all effort has been made completely to empty the uterus in order to permit it to contract down, and by its contraction to squeeze shut the bleeding sinuses and permit their occlusion by clots formed in the mouths thereof. Now, to reverse this physiologic effort to empty the uterus, and proceed to introduce a large mass of foreign material with the avowed purpose of stimulating the uterus to contract and of controlling bleeding by direct pressure of the foreign mass against the sinuses, necessarily mechanically held wide open by the pressure of that mass, does not seem to be good sense.

"If the uterus is so truly atonic as not to be capable of response to the mechanical stimulation of manual control already described and powerfully acting oxytocic, one can hardly expect that it will be capable of responding to the less efficient irritation of a wad of gauze pushed into it. If it does not so contract, it will merely balloon more and more as blood accumulates above the pack, and the supposed function of direct pressure of the packing against the whole surface of the uterus will be nullified. In this way the packing may do little more than stop the obvious flow of blood escaping from the uterus and lull the operator into a false sense of security."

As a last resort and rarely, when all the measures previously mentioned have failed, hysterectomy may be justified. Its justification is questionable in women who are exsanguinated, pulseless and do not have a readable blood pressure and have not had the benefit of massive blood replacement. This operation may in such cases hasten the death of the patient.

With massive blood replacement and a rapid hysterectomy, the operation becomes a life-saving procedure at times.

I merely mention the fact that hot and cold sterile douches have been used in protracted bleeding. In acute profuse bleeding such procedures as compression of the aorta and clamping of the uterine arteries from below have been instigated. Litzenberg aptly stated, "Excessive bleeding in the postpartum period is largely due to neglect—neglect of commission but principally of omission."

In modern obstetrics no woman should die from postpartum hemorrhage; however, to save a woman's life from death is not sufficient. Good obstetrics can reduce the incidence, quantity, mortality and morbidity of postpartum hemorrhage.

Bleeding from cervical and vaginal lacerations—These lesions should be definitely excluded even though the character of the bleeding may seem to be due to uterine atony. The cervix and vagina should be inspected and if lacerated should be repaired.

Retained placental remnants—Immediate postpartum bleeding is rarely due to retained placental remnants. At this point I wish to indicate the importance of thoroughly examining the placenta and membranes at the time of its delivery and if any part of the placenta is missing, it should be removed from the uterus. Retained placental remnants results in subinvolution, delayed hemorrhage and infection. Instrumental or digital removal of secundines may be justifiable in some instances.

Retention of placenta or retained placenta—By retention of the placenta is meant the failure of the placenta to be expelled one hour after delivery. This condition is thought of as a faulty uterine detachment with a faulty uterine muscular activity or behavior. Placental retention is seen in 1 per cent of all cases. If after one hour with massage and gentle downward pressure on the fundus there is failure in the placental expression, then manual removal is indicated.

There is certainly diversified opinion as to the dangers of manual removal. Specifically, there is a growing opinion that the danger of manual removal depends upon antecedent hemorrhage and infection. Then it would seem justifiable in the face of severe bleeding before placental separation to do a manual removal at once, and before the blood loss has reached a sizable amount such as 400 to 500 cc. Of course an opposite view in retention of the placenta without hemorrhage would be to ignore it, assuming its final detachment and passage. Hemorrhage and fatal sepsis may result. My recommendation is the manual removal of the placenta if it is not detached and expelled within an hour following delivery.

Placenta accreta—This is defined as an abnormal placenta, adherent to the uterine wall due to absent, scanty or faulty decidua with the choreonic villi penetrating deep into the uterine muscle. Clinically, the placenta fails to separate. Placenta accreta is associated with myomata uteri and syphilis. Manual removal is impossible and unjustified attempts at removal may result in uterine rupture. The treatment is hysterectomy.

Inversion of the uterus—The fundus becomes inverted and comes in contact with the cervix or may protrude through it and present at the vulva. The following considerations may be factors in this complication: marked thinness and laxity of the uterus at the placental site; a patulous cervix; pressure from above or traction on the cord or placenta; it is favored in fundal insertion of the placenta, and occasionally it occurs spontaneously, probably as a result of increased intra-abdominal pressure and possibly the weight of the intestines. The prognosis

is good if detected immediately; however, if it goes undiagnosed until gangrene occurs, the outlook is more serious.

The treatment is immediate reposition and if the placenta is not detached the uterus should be replaced with the placenta left on. A patient in considerable shock and in need of blood replacement should receive appropriate treatment and manipulation should be withheld until the general condition is improved. Shock is commonly due to the inversion, not to blood loss, and if the patient remains in shock after a reasonable amount of time, either manual replacement or the Huntington operation should be carried out. The latter operation is replacement by the abdominal approach. In both the short duration and the chronic long standing inversion, the Haultain operation in which the abdomen is opened and the cervical ring incised posteriorly may be the operation of choice. In chronic inversion the Spinelli anterior culpohysterotomy is also useful.

Retraction ring—This is not of serious consequence in the third stage of labor when the uterus contracts at the upper limit of the lower uterine segment. If no serious bleeding occurs, it is wise to await the relaxation of the uterine muscle which will occur in 10 to 30 minutes. If active bleeding occurs then, by necessity, one must direct his effort toward reduction of the ring and manual removal of the placenta.

Inasmuch as hemorrhage is first in the causes of maternal deaths and infection is a close second in maternal mortality, as listed in the Federal Security Agency of the United States Children's Bureau, it becomes evident that the third stage of labor with its attendant blood loss and likely infection in any one of the complications already considered becomes the most hazardous stage of labor and warrants the most meticulous handling, judgment and treatment.

In summary, it is not the first or second stage of labor that becomes the real risk for the mother, but the third stage with its attendant hemorrhage and possible infection. Hemorrhage is the number one killer of child-bearing women. A good dictum is "Save blood in the child-bearing woman."

Primitive incubators used in 1884. Temperature of babies was taken in a very crude manner by putting thermometer on their bodies.

Appendicitis and Cancer

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An analysis of cases has shown that cancer and appendicitis are more frequently associated than was previously noted. This concurrence of the two conditions has led to mistaken diagnoses and consequent improper treatment. The association between appendicitis and cancer is reviewed according to four possible relationships and procedures outlined for proper diagnosis and early treatment.

THE frequency with which cancer and appendicitis are associated as a diagnostic and therapeutic problem has prompted a review of cases at the St. Louis City Hospital, Barnes Hospital and Barnard Free Skin and Cancer Hospital. In the light of other reports on the subject[1-3] it is felt that the problem is commoner than is generally appreciated, and the following analysis, based on case histories, is presented to re-emphasize the need of being constantly aware of this possible association.

Carcinoma, whether primary or secondary in the appendix, may produce acute appendicitis by obstructing the lumen, by obstructing lymphatics or blood vessels, or both, or by infiltrating the wall. In such cases there is a danger of failing to recognize the basic disorder. However, there is an even larger group of cases in which primary carcinoma of the cecum produces symptoms and signs clinically indistinguishable from those of acute appendicitis. In this group the danger of unrecognized carcinoma of the cecum is great. The relationship between appendicitis and cancer may thus be any one of the following: (1) primary carcinoma of the appendix producing acute appendicitis; (2) metastatic carcinoma from a distant organ producing acute appendicitis; (3) primary carcinoma of the cecum producing acute appendicitis, or (4) primary carcinoma of the cecum producing clinical signs simulating acute appendicitis.

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PRIMARY CARCINOMA OF THE APPENDIX PRODUCING ACUTE APPENDICITIS

Primary adenocarcinoma of the appendix is rare. According to Lesnick and Miller[4] it occurs with about one-tenth the frequency of carcinoid of the appendix. These authors cited 12 cases from the literature and added 5 of their own. It is noteworthy that of these 17 cases, to which may be added the case reported by Marks and Whitaker,[5] the symptoms were those of acute appendicitis in 9 and of appendiceal abscess in 2. Pathologic examination showed that 5 appendixes of this series were also acutely inflamed, and 4, including the 2 diagnosed as appendiceal abscess, had perforated. Thus the preoperative diagnosis of acute appendicitis was made in half of the reported cases of primary adenocarcinoma and in about one fourth, acute appendicitis was also present. However, in no case was the diagnosis of appendiceal carcinoma made clinically.

Collins,[6] in a study of 3400 cases of acute ap-

pendicitis, found obstruction of the lumen to be the etiologic factor in 50 per cent.

It is therefore not surprising that primary carcinoma of the appendix should be so often associated with the symptoms of appendicitis and that appendicitis may frequently develop when cancer is present. Although in our series we did not have an example of primary adenocarcinoma of the appendix, the reports cited demonstrate the value of routine microscopic study of all appendixes removed. If such patients are to be offered the maximum hope for cure of the carcinoma, simple appendectomy is not sufficient and a resection of the terminal ileum and right side of the colon with their mesenteries must be performed.

COSTELLO

SAXTON

METASTATIC CARCINOMA FROM A DISTANT ORGAN PRODUCING ACUTE APPENDICITIS

Metastases to the appendix may occur in patients suffering from carcinomatosis peritonei, and in such instances the irritation of the appendix is a component of the clinical picture of general peritoneal irritation involving other areas as well. However, the appendix may be first involved by such a metastasis or may produce the first clinical evidence of disorder. The following is an example of such a case:

CASE REPORT

A 51-year-old white woman was admitted to the St. Louis City Hospital on January 31, 1950, with signs and symptoms of acute appendicitis. At operation the appendix appeared grossly inflamed and there was a small periappendiceal abscess. The appendix was removed and the abscess was drained. Microscopic examination of the appendix and a portion of omentum forming the abscess wall revealed an acute inflammatory exudate in all layers of the appendix and in the omental tissue. In addition, many of the subserosal lymphatics of the appendix and omental tissue contained nests of small epithelial cells, some in papillary arrangement and associated with small calcific (psammoma) bodies (Figure 1).

One month later the patient was re-explored and a bilateral salpingo-oophorectomy was performed, with removal of a piece of omentum. The ovaries were not enlarged, but firm, and each contained small cysts. Microscopic section of the ovaries showed in several areas small nests of epithelial cells together with many psammoma bodies. The cysts, which were both within the ovaries and on the surfaces, were lined with small cuboidal epithelial cells which formed simple papillary projections, often including psammoma bodies (Figure 2). The omental tissue contained nests of cells similar to those of the original specimen.

The tumor was regarded as an ovarian papillary cystadenocarcinoma, possibly bilateral in origin, of low grade malignancy with a tendency to local regression. The course of papillary cystadenocarcinomas of the ovary may vary considerably, as indicated by the report of Dunphy.[7] Four months later the patient returned to the clinic for routine examination. Although there were no complaints at this time, a small mass about 3 cm. in diameter was palpated on the posterior surface of the uterus. Obviously, the ultimate prognosis of patients with appendicitis associated with carcinomatous invasion from distant sites is poor.

PRIMARY CARCINOMA OF THE CECUM PRODUCING ACUTE APPENDICITIS

Burt,[8] in a comprehensive paper, stated that only 13 instances of carcinoma of the cecum complicated by appendicitis have been reported. He added 4 cases from the records of the Presbyterian Hospital, bringing the total to 17. Three such cases from the records of Barnes Hospital are here reported:

Case 1—This 57-year-old man was admitted in 1947 to Barnes Hospital complaining of epigastric pain which 10 days before had moved to the right lower quadrant. For the three days previous to hospitalization he had suffered generalized abdominal pains. Upon examination there was some generalized tenderness and involuntary muscle guard most marked over McBurney's point. Accordingly, the diagnosis of acute appendicitis was made and the abdomen was explored. A ruptured appendix with periappendiceal abscess was found and appendectomy was performed. Microscopic examination of the appendix revealed acute appendicitis and carcinoma of the appendix (Figure 3), thought possibly to have arisen from the cecum. One month later, exploration revealed a carcinoma of the cecum and right colectomy was accomplished (Figure 4).

Case 2—This 43-year-old woman was admitted to Barnes Hospital in 1944 complaining of intestinal cramping, nausea and vomiting for six hours. She had experienced episodes of discomfort in the right lower quadrant intermittently during the previous two years.

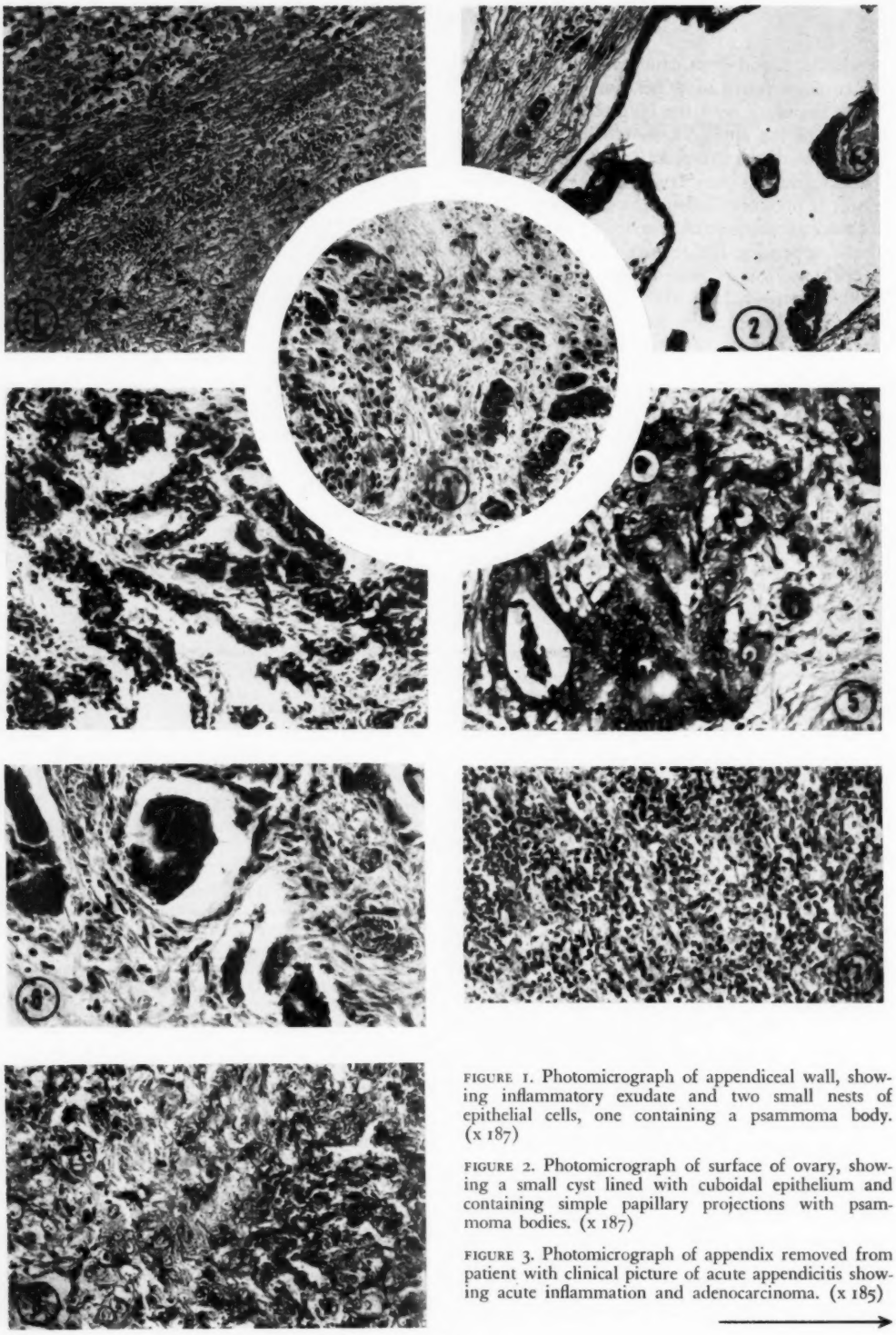

FIGURE 1. Photomicrograph of appendiceal wall, showing inflammatory exudate and two small nests of epithelial cells, one containing a psammoma body. (x 187)

FIGURE 2. Photomicrograph of surface of ovary, showing a small cyst lined with cuboidal epithelium and containing simple papillary projections with psammoma bodies. (x 187)

FIGURE 3. Photomicrograph of appendix removed from patient with clinical picture of acute appendicitis showing acute inflammation and adenocarcinoma. (x 185)

Upon examination there was found to be tenderness and muscle guard localized in the right lower quadrant, and the diagnosis of acute appendicitis was made. Appendectomy was performed and no suspicion of carcinoma existed until microscopic examination revealed carcinoma in addition to acute appendicitis (Figure 5). The patient was discharged and returned subsequently with signs of obstruction. A right colectomy was performed and a carcinoma of the cecum was removed (Figure 6).

Case 3—This 60-year-old woman was admitted to Barnes Hospital in 1945 presenting a history of a mass in the right lower quadrant for approximately eight months. Six months previously she had an episode of cramping pain in the right lower quadrant. Appendectomy had been performed at that time and the microscopic report was "acute appendicitis with abscess" (Figure 7). On this admission the patient was found on exploration to have had an extensive carcinoma of the cecum invading the abdominal wall (Figure 8). Because of the wide extension only biopsy was done.

AGAIN it should be emphasized that although in these cases carcinoma and acute appendicitis were proved to coexist, there are others, even more numerous, in which the patients are treated for appendicitis with or without surgical intervention and subsequently carcinoma of the cecum is found to have been the primary source of disorder. Thus the discussion of this group of cases may be included with that of the fourth and largest group where cancer and clinical appendicitis are associated.

PRIMARY CARCINOMA OF THE CECUM PRODUCING CLINICAL SIGNS SIMULATING ACUTE APPENDICITIS

One hundred and twenty-two cases of proved cancer of the cecum have recently been studied by one of us (C. C.) at the St. Louis City Hospital, Barnes Hospital and Barnard Free Skin and Cancer Hospital, and in 31 cases (25 per cent) appendicitis was the original diagnosis. In some of the patients, particularly where an abscess or a mass was present, carcinoma of the cecum was also considered, and careful exploration revealed the cancer, thus preventing the tragic consequences of mistaken diagnosis. However, in 16 patients, or 13 per cent of this group, treatment of appendicitis (usually appendectomy) without recognition or suspicion of the basic lesion had been performed prior to hospitalization for study and treatment of the carcinoma. These 16 patients varied in age from 28 to 72 years and represented delays in diagnosis of the carcinoma of from 1 to 36 months (Table 1). Almost half of this group were females and more than half were less than 50 years of age.

Since most of these patients had been treated for appendicitis elsewhere before admission to this group of hospitals, and since microscopic reports on the appendixes removed are not available, it must be assumed that the appendixes were inadequately examined or that the carcinoma had not actually extended into the appendix. Whether or not acute inflammation was present in these appendixes must also remain a matter of conjecture. Of importance is the fact that carcinoma of the cecum was not recognized in these patients. Such an error may result from the following pitfalls:

1. Failure of the surgeon to examine the cecum carefully at the time of appendectomy.
2. Inability of the surgeon to distinguish carcinoma of the cecum from coincident inflammation.
3. Failure to take tissue for biopsy from suspected areas.
4. Failure to have the appendix examined microscopically at several levels.
5. Failure of the inexperienced surgeon to proceed with definitive cancer surgery even after recognition of the lesion.
6. Failure to perform adequate follow-up diagnostic studies on that small group of patients treated nonsurgically for appendicitis.

Thus, from this study it is apparent that 25 per cent of patients with carcinoma of the cecum presented signs of appendicitis. This is in agreement with the observation of Ackerman,[1] although higher than that of Ransom.[3] In nearly half of these the carcinoma was recognized at operation or by pathologic examination of the appendix, whereas in the remainder

FIGURE 4. Photomicrograph of mucinous carcinoma of the cecum from same case as Figure 3. (x 185)

FIGURE 5. Photomicrograph of the appendix in Case 2. Both acute appendicitis and carcinoma are present. (x 185)

FIGURE 6. Photomicrograph of carcinoma of cecum removed from patient in Figure 5. (x 185)

FIGURE 7. Photomicrograph of representative area of appendix (Case 3) showing acute appendicitis. This appendix was removed and a small periappendiceal abscess was drained. (x 185)

FIGURE 8. Photomicrograph of biopsy specimen of carcinoma of the cecum removed six months later from the patient whose appendix is shown in Figure 7. (x 185)

TABLE 1

PATIENTS TREATED FOR APPENDICITIS PRIOR TO RECOGNITION OF CARCINOMA OF THE CECUM

CASE	AGE	SEX	DIAGNOSIS	TIME BETWEEN TREATMENT OF APPENDIX AND RECOGNITION OF CANCER OF THE CECUM (MONTHS)	TREATMENT
1	60	F	Appendicitis	2	Appendectomy
2	28	M	Appendicitis	2	Nonsurgical
3	59	M	Appendicitis	24	Nonsurgical
4	62	M	Appendiceal abscess	2	Drainage of abscess
5	43	F	Appendicitis	1	Appendectomy
6	60	M	Appendicitis	6	Appendectomy
7	39	M	Appendicitis	18	Appendectomy
8	39	M	Appendiceal abscess	7	Drainage of abscess
9	37	M	Appendicitis	5	Appendectomy
10	29	F	Appendicitis	2	Appendectomy
11	72	F	Appendicitis	2	Nonsurgical
12	43	M	Appendicitis	6	Appendectomy
13	48	F	Appendicitis	36	Appendectomy with no relief of symptoms
14	65	F	Appendicitis	12	Appendectomy
15	47	M	Appendicitis	7	Appendectomy
16	39	F	Appendicitis	18	Appendectomy

the carcinoma was not found for months afterward. In this latter group, advancement of the carcinoma might have been avoided by better realization of the possibility of the dual lesion and by more careful and persistent search and study.

The intimate anatomic relationship between appendix and cecum predisposes to easy involvement of the appendix by a carcinoma originating in the cecum. And, similarly, the clinical manifestations of carcinoma arising in the cecum may be easily misinterpreted as acute appendicitis. Since appendectomy alone is not adequate treatment for carcinoma of the appendix or cecum and since many of these lesions at the initial illness interpreted as appendicitis are resectable and curable, it is mandatory that the possibility of a dual lesion be constantly borne in mind. Awareness of the possibility, especially in relatively young persons of either sex, should reduce the incidence of unrecognized cecal carcinoma.

In patients presenting appendicitis with the gross suggestion of carcinoma arising in the cecum (by virtue of pericecal abscess or mass) exploration of the cecum by incision at the time of appendectomy may be valuable. In those in whom the appendix is removed, careful pathologic study of the appendix, particularly of its base, should be insisted upon routinely. In patients who present recurring episodes of appendicitis, appendectomy and exploration should be performed. Errors in recognition of carcinoma of the cecum will unquestionably occur in higher incidence when appendectomy is performed by surgeons untrained in pathology and in surgical technic. When the lesion is recognized the definitive treatment for operable carcinoma of the cecum is right colectomy with ileotransverse colostomy. In those instances in which there may be associated bowel obstruction or where the general condition of the patient is poor, it may be necessary to perform the colectomy at a subsequent surgical stage.

REFERENCES

1. ACKERMAN, L. V., and DEL REGATO, J. A.: Cancer. St. Louis, C. V. Mosby Company, 1947.
2. UIHLEIN, A., and MCDONALD, J. R.: Primary carcinoma of the appendix resembling carcinoma of the colon. Surg., Gynec. & Obst. 76:711-714, 1943.
3. RANSOM, H. K.: Carcinoma of the right colon. Surgery 5:340-357, 1939.
4. LESNICK, G., and MILLER, D.: Adenocarcinoma of the appendix. Cancer 2:18-24, 1949.
5. MARKS, E. S., and WHITAKER, H. W.: Primary adenocarcinoma of the appendix. Surgery 27:720-725, 1950.
6. COLLINS, D. C.: Etiological factors in acute appendicitis. Surgery 5:267-270, 1939.
7. DUNPHY, J. E.: Some observations on the natural behavior of cancer in man. New England J. Med. 242:167-172, 1950.
8. BURT, C. A.: Carcinoma of the cecum complicated by appendicitis or para-cecal abscess. Surg., Gynec. & Obst. 88:501-508, 1949.

Diagnostic Clinic

The Diagnosis and Treatment of Ileitis

CHARLES W. MAYO*

MAYO CLINIC, ROCHESTER

Regional enteritis is a chronic nonspecific granulomatous inflammation primarily of the terminal part of the ileum. The cause is unknown. Medical treatment consisting of measures of a supportive nature should be tried first. If this fails after adequate trial, then surgical treatment must be considered in a high percentage of cases.

I AM to talk to you on regional enteritis and I should like first to give you histories of the three ladies who have kindly consented to appear before you.

The first is Mrs. H., who is 35 years old, married, and was admitted to the surgical clinic in 1949 complaining of low-back pain, nausea and vomiting; the attacks of low-back pain were unrelated to meals or activity. She had had these symptoms for about a year. The attacks began with throbbing lumbar pain accompanied by borborygmi and visible peristalsis. She then became nauseated and vomited, the vomiting lasting for two or three hours; it started with partially digested food and progressed to yellowish brown fecal material. Following the vomiting she felt better and the back pain subsided.

The attacks became progressively more frequent. At the time of admission they occurred weekly. There was never any jaundice, hematemesis or melena. She lost 20 pounds during the year before admission to the clinic.

The past history is that of a tonsillectomy at the age of 12 and an appendectomy at the age of 17.

The temperature was essentially normal, the pulse 80, and the blood pressure 110 systolic and 64 diastolic. Physical examination revealed a small, pale woman in no distress at that time. The only significant finding was tenderness in the right upper abdominal quadrant and pain in the right costovertebral angle. No masses were palpated. The results of urinalysis and serologic tests for syphilis were normal. The red blood cells numbered 3,400,000 and the white blood cells 9500 per cubic millimeter of blood; the hemoglobin content was 9.8 gm. per 100 cc. Barium examination of the stomach and duodenum gave normal results; cholecystography revealed three large radiolucent calculi, and barium enema examination showed an irritable cecum and failure of the terminal part of the ileum to fill.

The clinical diagnosis of cholecystitis and cholelithiasis was made. Celiotomy revealed stones in the gallbladder and a partially obstructive regional ileitis. The terminal portion of the ileum was thickened, and the mesentery was edematous. The terminal 14 inches of the ileum were excised and an ileocecostomy was done. Recovery was uneventful. The patient subsequently had a cholecystectomy. This first operation of resection of the terminal portion of the ileum was done late in October, 1949.

She tells me that her weight has increased from 79 to 106 pounds since that resection and she also tells me that she can eat anything now. Correct?

PATIENT: Yes.

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CHARLES W. MAYO

DR. MAYO: The next patient is Mrs. G. She is 32 years old, married, and was admitted to the surgical clinic in September, 1949, complaining of epigastric pain and vomiting. The patient reported that she had been well until four days before admission, at which time she experienced the sudden onset of crampy epigastric pain shortly after the noon meal. The pain lasted for two hours and then subsided. Two days later the pain recurred and continued for about 24 hours, associated with nausea and vomiting.

When she was admitted to the clinic she was dehydrated. Her abdomen was distended and she showed carpopedal spasm. There had been no previous operations. The temperature was normal as were the blood pressure and pulse.

Physical examination revealed a well developed Negress in marked distress. Her skin was dry and her tongue coated. The abdomen showed moderate distention, deep tenderness, but no muscle guarding or rebound tenderness. No masses could be palpated. The bowel sounds were hyperactive. The urine, the number of red blood cells and the results of serologic tests for syphilis were all essentially normal.

Decompression was done with a Harris tube and nutrition was maintained by parenteral therapy. The symptoms were relieved by suction but were aggravated when the tube was clamped.

Celiotomy revealed marked edema and congestion of the terminal portion of the ileum and the mesentery. The terminal 18 cm. of ileum were excised and ileocecostomy was done. Her recovery was uneventful.

Mrs. G. tells me that she can now eat anything and feels in excellent condition. She has gained some 10 pounds since her operation.

THE other lady, Mrs. S., is 26 years old, married, and entered the surgical clinic complaining of severe lower abdominal pain. The patient reported that she had not been well for seven months. At that time she first experienced a heavy feeling in the right lower quadrant after meals and a dull aching pain which at times became colicky in nature. The attacks persisted for several hours, at times with associated abdominal distention. On several occasions she had more severe pain accompanied by chills and fever.

During such an attack three months ago she was admitted to the hospital and celiotomy was done for chronic appendicitis. At operation there was free fluid in the abdominal cavity, the ileum was congested and indurated and the mesentery contained many large nodes. Appendectomy was performed. Postoperatively the symptoms persisted, and for the week before admission she had diarrhea almost constantly. She had lost 15 pounds since the onset of her disease.

Physical examination revealed a well developed female with a temperature of 98° F., pulse 100, respirations 20, skin and mucous membranes pale. Significant physical findings were limited to the abdomen. A lower abdominorectal scar was present beneath which an irregular tender mass measuring 4 by 5 cm. was present. The borders of the mass were poorly defined and it was somewhat confined to the posterior abdominal wall.

The urine, hemogram and the results of serologic tests for syphilis were all normal. Barium examination of the colon revealed no abnormality. Barium examination of the ileum disclosed inability to visualize the terminal portion. This was thought to be compatible with terminal ileitis.

She has not as yet been operated upon. At the present time she is getting 15 gr. (1 gm.) of SULFATHALIDINE® four times a day.

The definition of regional enteritis is that of a chronic nonspecific granulomatous inflammation primarily of the terminal part of the ileum, which may spread proximally, directly or by skip areas. It may also spread distally to involve the colon.

There are many synonyms for regional enteritis, such as regional ileitis, terminal ileitis, Crohn's disease, phlegmon of the ileum, nonspecific enterocolitis and segmental enteritis.

Dr. Crohn thinks that the incidence of regional enteritis is about 50 per cent of that of chronic ulcerative colitis.

Much research work has been done on this subject. The disease must have some inflammatory background, but up to date there has been nothing to which it can be specifically attributed. *Bacillus dysenteriae,* coliform strains, microbacteria and many saprophytes have been studied. Toxins, viruses and protozoa have been considered as possible causative agents. Lysozyme also has been considered one of the possible etiologic factors in terminal ileitis as well as in chronic ulcerative colitis, the concept being that this substance digests the mucous membrane and allows it to become susceptible to the secondary infections which come along. Allergy is another one of the possible etiologic factors which has been studied. The neurogenic factor is an important one here, as is also true with chronic ulcerative colitis.

Nothing is known at present that one can say is the cause of regional enteritis, any more than one can say that there is a specific etiologic factor known today in ulcerative colitis.

FIGURE 1. Regional enteritis showing distention and thickening of the bowel wall.

Because we have no known etiologic agent, study of chronic ulcerative colitis and of terminal ileitis has been confined to the clinical level and consequently has all the limitations of clinical investigation. There is a wide variability and there are wide degrees of severity; necessarily, then, large series have to be studied to permit making any definite—and, I am sorry to say, not too definite—conclusions.

When one obtains good results with a medical regimen one wonders why. When one obtains good results from certain specific technics and a surgical approach to the problem one again wonders why, because there is a fairly high percentage of recurrences.

The pathologic features of this disease involving the bowel wall are thickening, a narrowing of the bowel lumen, degrees of mucosal ulceration, destruction and hyperplasia. Submucosal lymphatic hyperplasia varies but is present in about 95 per cent of the cases. Characteristically the lymph nodes are enlarged and discrete giant cells are present but there is no caseation and no acid-fast organisms are present.

As to the symptoms, Dr. Melton, a fellow of the Mayo Foundation who reviewed carefully 103 proved cases in his thesis, reported that abdominal pain occurred in 96 per cent of the cases, diarrhea in about 65 per cent, obstruction in 51 per cent, fever in 33 per cent and blood in the stools in 12 per cent.

Figure 1 shows a resected specimen in which the ileum above is distended and there is thickening of the bowel wall. This is a regional affair. It also shows why there is obstruction.

Figure 2 shows the relationship between ulcerative colitis and terminal ileitis. In about 28

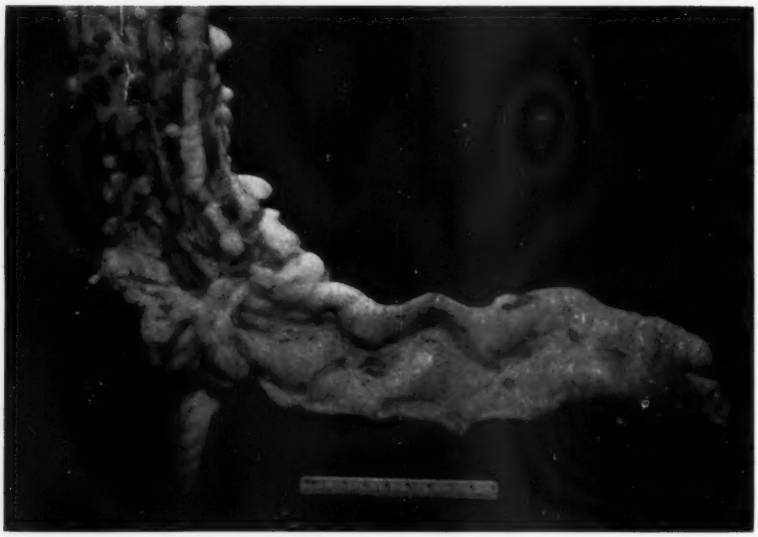

FIGURE 2. This illustrates the relationship between ulcerative colitis and terminal ileitis. In addition, pseudopolyps are visible in the ascending colon.

per cent of the cases of ulcerative colitis there is involvement of the terminal part of the ileum. It is also true, as I brought out in the definition of this disease, that with regional or terminal ileitis the colon is frequently involved and the disease will be seen sometimes to extend all the way to the sigmoid. We used to think that in 5 per cent of the cases of ulcerative colitis the disease started in the right portion of the colon.

THERE is one point that probably has not been stressed enough, and that is that even with terminal ileitis or regional ileitis, on proctoscopic examination one can find, in a fairly high percentage of these cases, petechial hemorrhages in the rectum.

The signs and symptoms of either chronic, subacute or acute appendicitis are present. It is to be noted that in one of the patients presented the appendix had been removed some three months previously. It so happens that in about 50 per cent of these cases of terminal or regional ileitis the appendix has been removed in the past, and sometimes appendectomy has been performed very shortly before an operation has to be done for the ileitis which occasionally is the primary cause of the symptoms.

Terminal or regional ileitis occurring in the terminal portion of the ileum is not infrequently, following appendectomy, the cause of abdominal fistula.

I have shown you why there is mimicry of actual ulcerative colitis in this particular disease process. There are possibly signs of nutritional anemia, hypoproteinemia with edema, pellagra and scurvy, and these occur because of the nutritional disturbances.

From the laboratory standpoint, hyperchromic anemia occurs in about 50 per cent of the cases, and occult blood is found in 60 per cent in contrast to frank hemorrhage which, as I said, occurs in 12 per cent.

The roentgenologic examination is a valuable adjunct to diagnosis. Barium and contrast films are used. One can differentiate amebic dysentery very readily from terminal ileitis because with amebic dysentery there is a sludging back and forth of the barium between the cecum and the terminal portion of the ileum.

Where terminal ileitis is found with the aid of barium administered by rectum and colon, one has also to consider that it is important to do a barium-by-mouth examination of the entire small intestine because of the danger of skip areas in this particular disease.

As to age and sex, it will be noted that of the 3 patients presented, 1 was 26 years old, 1 was 35, and 1 was 32, and all were females. The average age for regional enteritis is around 29. It is a disease of fairly young people as is ulcerative colitis. As a matter of fact, in 75 per cent of the cases the disease occurs between the ages of 20 and 40. There are 3 males to 2 females,

which is in accord with the fact that the male usually predominates in everything except diseases of the womb.

The average duration of symptoms before the diagnosis is made is 17 months.

From a differential diagnostic standpoint, regional enteritis can mimic amebic dysentery, tuberculous granuloma, irritable bowel syndrome, intestinal tumor, carcinoma, carcinoid, lymphoblastoma, myoma, sarcoma, fibroma, actinomycosis and appendicitis; frequently the diagnosis is not made until operation is undertaken.

From the standpoint of medical treatment, since there is lack of specific measures, the management must be of a supportive nature: (1) mental and physical rest; (2) diet, and in diet one should keep in mind that there should be a high-carbohydrate, high-protein and low-fat intake; (3) intake of the water-soluble vitamins, the B complex and C, in large amounts; (4) the giving of calcium lactate or gluconate; (5) use of tincture of belladonna, bismuth, kaolin, and avoidance of narcotics for diarrhea; and (6) the use of chemotherapeutic or antibiotic agents; while no definite proof of value yet exists, I believe that these agents may well have a place in the medical therapy of this disease process.

From the surgical standpoint, I think that all these patients should have medical treatment first. There must be in regional enteritis—and we do run into such patients—the subclinical type of disease which is self-limiting and not diagnosed accurately, just as there are attacks of poliomyelitis which are subclinical; nevertheless, if, after a trial of medical treatment for a time, symptoms are getting worse and are occurring with increased frequency, eventually surgical treatment has to be considered in a high percentage of cases.

The question comes up as to whether surgical treatment should consist of resection or a sidetracking procedure. If there is no obstruction I think that one can consider sidetracking the ulcerative process by doing an inversion in the good bowel of the ileum, well above the involved portion, and doing an end-to-side ileotransverse colostomy. There is a lot of evidence that a sidetracking procedure, in which there is a complete sidetracking, does bring about a quiescence, at least, of the disease process. There is considerable evidence also that resection is a good procedure to follow.

Although it is too short a time to say and the future will tell, I hope that in these 3 patients presented here there will not be a continuation of the process, although all who operate on such patients know that most get along well for some time but too many come back with recurrence.

As far as I am concerned I think that, in view of the aid available from antibiotic preparations, we are going to incline more and more to resection in these cases. The most important thing from a surgical standpoint in resection is to get well beyond the involved portion in the colon if it has gone through the ileocecal valve, and certainly well beyond the involvement in the ileum, and then to perform the anastomosis either as an end-to-end procedure, which I usually do, or as an end-to-side procedure. The ileum may be anastomosed with the ascending colon, the transverse colon or even the more distal part of the colon when such is necessary to get beyond the diseased part. An accurate anastomosis without tension is essential.

In conclusion I should like to say that at the clinic cures are obtained in 50 per cent of the cases regardless of the type of surgical treatment used. In 25 per cent there is a fair result, in 25 per cent there is failure with the first operation, but of those cases in which reoperation is done a cure is obtained in 50 per cent.

It is to be hoped that still more minute study of individual cases and further investigative research will bring to light the causative agent not only of regional enteritis but also of ulcerative colitis. It is my feeling that eventually we will find that the etiologic agents in these two disease processes are very closely related.

Diagnostic Clinic

The Syndrome of Large, Pale Ovaries and Its Differentiation from Adrenogenital Syndrome and Cushing's Disease

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Patients with large, pale ovaries (Stein-Leventhal syndrome) usually complain of amenorrhea, sterility and hirsutism. Recognition of this syndrome is important since the amenorrhea and sterility may frequently be corrected by wedge resection of the ovaries. Cushing's disease, adrenogenital syndrome, arrhenoblastoma and idiopathic hirsutism must be considered in diagnosis.

The practicing physician is often confronted by the hirsute amenorrheic woman who seeks his advice. He finds himself in the dilemma of deciding whether a particular case is one which may be classified as belonging to the syndrome of "large, pale ovaries," the adrenogenital syndrome, Cushing's disease or is simply one of idiopathic hirsutism. The differential diagnosis, puzzling though it may frequently be, may be simplified by an appreciation of the various syndromes mentioned.

THE SYNDROME OF LARGE, PALE OVARIES

Stein and Leventhal[1] in 1935, drew attention to a syndrome of amenorrhea associated with the presence of bilateral cystic ovaries. Since then Stein[2-4] has collected and faithfully followed a large series of cases and has repeatedly drawn attention to this syndrome. The symptoms listed by Stein and his associates[4] which prompt the patient to seek advice are, in order of their frequency: (1) amenorrhea, (2) sterility, (3) hirsutism, (4) pain (rarely) and (5) menometrorrhagia (occasionally).

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A valuable diagnostic sign is the finding of bilateral and symmetrically enlarged ovaries either on palpation or by pneumoperitoneum. At laparotomy the ovaries are large, smooth, elongated and freely movable (Figure 1). The Stein-Leventhal syndrome of bilateral polycystic ovaries has been spoken of as sclerocystic disease and microcystic disease of the ovaries and was given the descriptive designation of "large, pale ovaries" by Albright.

Histopathology—On sectioning the ovaries numerous small cysts usually occupy the cortex (Figure 2). Occasionally, a corpus luteum cyst may also be found. Microscopically, a thick fibrous capsule is characteristic and is usually associated with increased fibrosis of the ovary and hyperplasia of the theca cells. In the cortex, scattered primordial follicles may be found (Figure 3). At other times these are so scant as to appear absent (Figure 4). Many follicular cysts are usually in evidence. Many of these are lined by varying layers of granulosa cells surrounded by several layers of hypertrophic theca cells (Figure 5). Some of the follicles, however, show loss of the granulosa cell layers and the wall of the follicle shows hyalinization (Figure 6). Evidence of an occasional old corpus luteum cyst or a corpus albicans may be present. Corpora atretica are frequent.

Etiology of the disorder—In 1942 Geist and Gaines[5] drew attention to 2 cases of masculinizing syndrome with enlarged ovaries. Histologically, the ovaries showed excessive perifollicular proliferation, luteinization of the theca cells and diffusely scattered patches of luteinized cells within the ovarian parenchyma. The ovarian effects were suggestive of increased gonadotropic stimulation and were probably secondary. To them, these findings implied primary dysfunction or hyperfunction of certain components of the anterior pituitary gland as the cause of this disorder. Culiner and Shippel[6] presented further evidence of a concurrent relationship between theca cell hyperplasia in the ovary and masculinization. They observed 3 patients with hirsutism, amenorrhea and sterility with bilateral enlargement of the ovaries. An enlarged clitoris was present in each of their cases. In the series reported by Stein, the external genitalia in most patients were normal, but in some the labia minora and clitoris were markedly hypertrophied.

In the presence of such virilizing signs as enlargement of the clitoris or voice changes, one should show utmost caution in entertaining a diagnosis of large, pale ovaries. Extensive studies are warranted to rule out early Cushing's disease, the adrenogenital syndrome or arrhenoblastoma.

Meaker[7] believed as Zondek does that the fundamental cause of microcystic disease of the ovary is probably a phase of hypergonadotropism. Under normal conditions large numbers of primordial follicles start to mature but never complete the process. Under the influence of excessive pituitary stimulation, however, numerous follicles are stimulated. At some point along the way, the ova die, whereupon the follicles regress and ultimately become insignificant corpora atretica. Greenblatt, Pund and Torpin produced changes in the human ovary not unlike those seen in this syndrome by the administration of large doses of gonadotropins.[8,9] Aside from follicular stimulation, marked theca cell hypertrophy with luteinization and indistinct activation of patches of theca-like cells in the ovarian stroma were consistently obtained.[10]

Ingersoll and McDermott[11] were impressed with the variety of menstrual disorders that occur with this syndrome. In 13 of their 21 cases there was either amenorrhea or oligomenorrhea, while in 8 patients there was excessive uterine bleeding. In 4 of these 8 patients the menorrhagia occurred after many months of amenorrhea. These authors felt that the etiology of the disorder was obscure but suggested two likely possibilities: (1) congenital fibrosis and thickening of the ovarian capsule produce a mechanical barrier to ovulation resulting in polycystic changes; (2) primary hormonal imbalance, possibly in the secretion of luteinizing hormone by the pituitary, produces secondary changes in the ovary.

ROBERT B. GREENBLATT

AUTHOR'S SERIES

For several years the author has been aware of this syndrome and has accepted it as an entity. In the past year, however, a more thorough study from the endocrinologic point of view was undertaken in 10 patients. The following findings in this small series appear to be significant:

1. The patients were quite feminine in attitude and aptitude. In all, the body habitus was definitely feminine and all had unusually well developed breasts (Figure 7).

2. Hirsutism in varying degree from moderate to excessive was present in all cases of this series. Other evidence of masculinization, however, was not to be found—such as enlargement of the clitoris or voice changes.

3. Menstrual disorders such as amenorrhea or

menorrhagia following periods of amenorrhea were noted in each case.

4. The vaginal cytology usually revealed either estrogenic, progestogenic or androgenic smears.[12] Endometrial biopsies revealed either a persistent estrogenic endometrium or a cystic glandular hyperplasia. In only one case of this series was a progestinal endometrium obtained and this patient at laparotomy had a current corpus luteum following a period of several months of amenorrhea.

5. At laparotomy all showed the characteristically large, pale ovaries and histologically all showed abiotrophy of the ovaries,[13] and in only one was evidence of a recent corpus luteum found.

6. Urinary 17-ketosteroid values were normal in 7, moderately elevated in 3. Urinary 11-oxycorticoid values were normal or low in the 7 patients in whom the test was performed. The urinary gonadotropins were elevated in 4 and normal in 2 others. Attempts to prove the presence of excess luteinizing hormone with the methods available were made in 3 patients. In 2, positive values were obtained.

7. Evidence of the syndrome manifested itself early in adolescence in many of our cases but became well defined between the second and third decades of life. The ages in our series ranged from 13 to 32 years.

8. The desire for conception was strikingly singular in the 6 married patients in this group, all of whom complained of sterility.

TREATMENT

Wedge-shaped resection of the ovaries is, in a great number of instances, accompanied by resumption of cyclic ovulatory menstruation. In Stein's series infertility was overcome in 73.8 per cent of the cases following this operation. Hirsutism, however, which was present in over 60 per cent of their patients, was not usually affected favorably. In a few patients excess hairy development disappeared to a remarkable degree. Meaker[7] operated on 65 patients with this syndrome because of sterility and menstrual disorders. Sixty-six per cent of infertile women conceived and 77 per cent of the menstrual disorders were relieved.

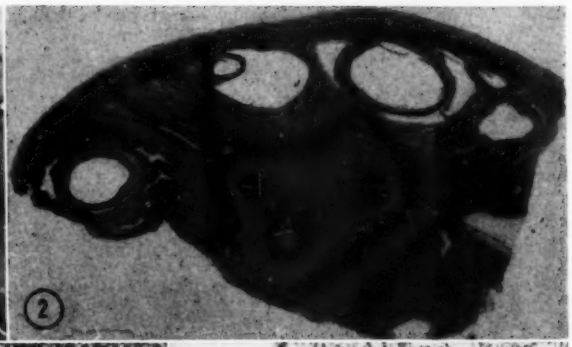
THE ADRENOGENITAL SYNDROME

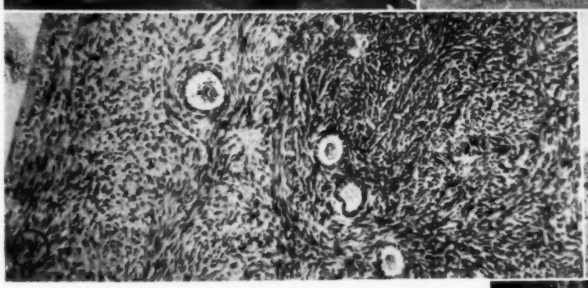
The adrenogenital syndrome in the broadest sense of the term comprises all the conditions in which abnormal changes in the sexual and metabolic sphere are referable to organic or functional disturbances in the adrenal cortex. In this paper, however, adrenogenitalism is employed in the narrower sense and refers to true masculinization of the female due to hyperactivity of the corticosexual group of adrenal hormones. This syndrome is closely simulated by masculinizing tumors of the ovary.

Symptomatology—The signs and symptoms of the adrenogenital syndrome will depend on the time of development of the adrenal disorder (Figure 8). When the lesion occurs in prenatal life the picture is usually that of pseudohermaphrodism. In such instances the clitoris enlarges so as to resemble an hypospadiac penis. The vagina is absent or rudimentary (Figure 9). Physical configuration, hair distribution and psyche are masculine. The internal genitalia, uterus, tubes and ovaries remain infantile. If the onset occurs later in puberal life the masculinization is usually less complete. Precocious puberty with enlargement of the clitoris and labia majora, appearance of pubic hair and hirsutism may occur. Sometimes breast growth and menstruation may be found. The powerful muscular development seen in male precocity, the "infant Hercules," is not seen in the female though minor degrees may be observed.[14-18]

When the syndrome becomes established in adult women after puberty hirsutism, amenorrhea, lowering of pitch of voice and/or enlargement of the clitoris and, at times, increased muscular strength, set in (Figure 12). When all these signs and symptoms are present true virilism is said to exist.

Diagnosis—The adrenogenital syndrome is in many ways the exact antithesis of Cushing's syndrome. In this syndrome (adrenogenitalism) the excess corticoids conserve protein instead of converting protein into sugar. Sugar metabolism is usually not disturbed. Obesity is not the rule. Hypertension is usually absent. The diagnosis is confirmed by normal glucose and insulin tolerance tests. Urinary assays of 17-ketosteroids range from 40 to 150 mg. per 24-hour specimen but may reach 1000 or more milligrams.[19] The 11-oxycorticoids are usually normal. Urinary excretion of beta-ketosteroids such as dehydroisoandrosterone is usually markedly elevated in patients with adrenal cortical tumors but not with adrenal hyperplasia.[20] Retrograde or intravenous pyelograms are helpful (Figure 13). The presence of an adrenal tumor may be sus-





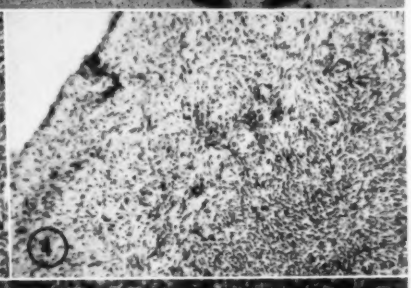


FIGURE 1. Note the bilaterally elongated, enlarged pale ovaries.

FIGURE 2. Photomicrograph of transected section of ovary. Note the numerous small cystic areas occupying the cortex.

FIGURE 3. Note the thickened zone of fibrosis in the cortex extending to the surface making for a thick capsule with scattering of primordial follicles.

FIGURE 4. At other times primordial follicles are so few as to appear absent.

FIGURE 5. Note hyperplasia of theca cells surrounding follicle lined by several layers of granulosa cells.

FIGURE 6. Note early hyalinization of walls of atretic follicles.

FIGURE 7. Note the hypertrichosis of chin and breasts in association with well developed breasts.

FIGURE 8. Adrenogenital syndrome. Note the masculine distribution of sexual hair, the male body habitus, the cephalic alopecia. The patient's aptitudes and attitudes were those of a male.

FIGURE 9. Note the rudimentary vagina and the hypospadiac penis of patient shown in Figure 8. Laparotomy revealed presence of ovaries.

FIGURE 10. Conversion of female pseudohermaphrodite shown in Figures 8 and 9 into a male by closure of vagina and plastic reconstruction of penis.

FIGURE 11. Happy ending. Pseudohermaphroditic female converted to status of happily adjusted male.

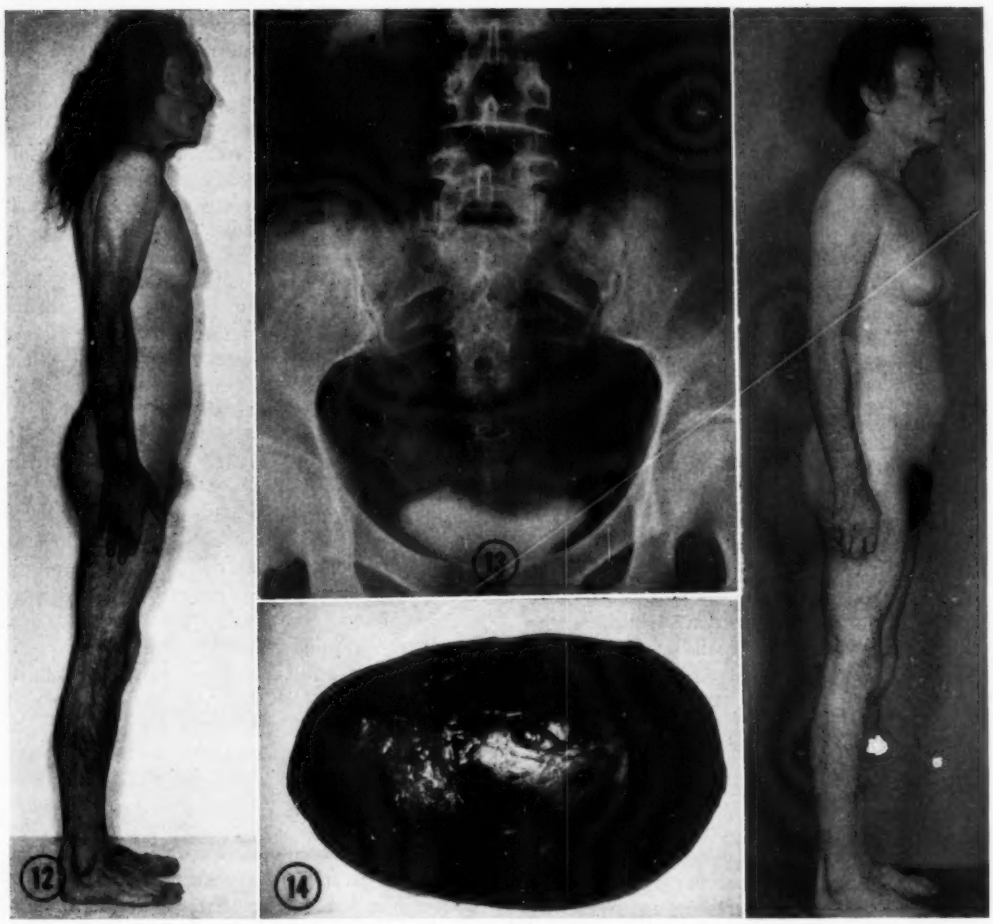


FIGURE 12. Adrenogenital syndrome in adult female aged 40. Note hypertrichosis, masculine body build, atrophic breasts. The clitoris was moderately enlarged. Urinary 17-ketosteroids were 1257 mg. per 24-hour specimen.

FIGURE 13. Note displacement of right adrenal by large adrenal tumor (intravenous pyelogram).

FIGURE 14. Adrenal tumor removed from patient shown in Figure 12.

FIGURE 15. Eight months after removal of tumor. Contrast with Figure 12. Note the breast development, restoration of female bodily build, decrease in bodily hair. There was return of cyclic menstruation with ovulation. Urinary 17-ketosteroids studied at monthly intervals have remained at normal levels for the past eight months, averaging between 8.8 and 14.8 mg. per 24-hour specimen.

pected if there is distortion of the calyces and rotation and displacement of the kidney. If, on pelvic examination, a solid ovarian tumor is palpable, one should suspect that the symptoms of adrenogenitalism are not due to adrenal pathology but to an arrhenoblastoma or so-called hypernephroma of the ovary.

Therapy—The therapy of choice where an adrenal tumor is found is surgical removal (Figure 14). In females, when unilateral tumors are removed, many of the signs and symptoms gradually disappear and restitution of gynecic function may be expected (Figure 15). Where adrenal hyperplasia exists one may resort to bisection of each adrenal gland. The results, however, have not been encouraging. Removal of one whole adrenal gland and part of the other is more radical but has proved in some hands a

worthwhile though most formidable undertaking.[21] In congenital adrenal hyperplasia associated with hermaphrodism it is preferable to convert the patient into the sex for which the patient is best suited psychologically and emotionally (Figures 10 and 11).

CUSHING'S DISEASE AND SYNDROME

In Cushing's disease as in Cushing's syndrome, the main physiologic disturbance is one of hypergluconeogenesis. The fundamental disorder is in the adrenal in both, but in the former it is intrinsic while in the latter it is secondary to excessive pituitary stimulation of the adrenal. The overproduction of corticometabolic hormones results in disturbances of carbohydrate, fat and protein metabolism. A negative nitrogen balance is present and there is excessive storage of fats. Excessive protein loss is due to hypergluconeogenesis which results from the overproduction of the 17-hydroxycorticosterone group of hormones.[22] Cushing's disease is primarily a metabolic disorder, while adrenogenitalism is primarily a disturbance in the sexual sphere. In Cushing's syndrome, signs and symptoms simulate those of Cushing's disease.

Symptomatology—The cardinal features found in Cushing's disease are obesity, hypertension, atrophy of the skin, depression of gonadal function, decreased sugar tolerance, erythrocytosis, osteoporosis, fatigability and weakness. Other complications frequently observed are cardiac decompensation, chronic nephritis and nephrolithiasis. The obesity usually encountered is that of the buffalo type, i.e., confined to face and trunk and sparing the extremities (Figure 16). The abdomen may protrude giving the appearance of girdle obesity. This apparent girdle obesity results more from the relaxation of the abdominal wall than from the actual deposition of fat. However, generalized obesity may be encountered. The blood pressure is usually very high but may be of the fluctuant type. Hypertrichosis of the face and chest and masculine distribution of pubic hair are conspicuous features. Manifestations of atrophy of the skin are common findings. The plethoric appearance in most of these patients is thought to be due to the transparency of the skin. The purplish striae and purpuric spots result from poor skin matrix (Figure 17). The skin manifestations are part of a widespread tissue atrophy due to protein deprivation.

As the disease progresses, gonadal regression sets in. Regressive ovarian function is reflected in amenorrhea, atrophic endometrial changes and in castrate vaginal smears. Libido is diminished or absent. Osteoporosis, particularly of the vertebrae, has been reported in many cases. Collapsed vertebrae, kyphosis and lumbar pain are common features. The decalcification is not primarily a calcium disorder but the result of a lack of bone matrix. The moderately rapid loss of calcium not infrequently results in nephrolithic calcium deposits. Fatigability, asthenia and marked weakness are features of the disease due to decreased muscle mass and negative nitrogen balance.[23] Hyperglycemia and glycosuria are frequently found. In many the fasting blood sugar is normal but when a glucose tolerance test is performed a decreased sugar tolerance curve is obtained. On performing the insulin tolerance test, hypoglycemia does not result after intravenous injection of insulin.

Diagnosis—The hirsutism is usually not attended by other signs of true virilism such as enlargement of the clitoris or voice changes. However, in some instances there is a tremendous overlapping of the adrenogenital and Cushing's syndromes so that the patient is both virilized and has all the signs and symptoms of the metabolic disorders common to Cushing's disease. In the pure cases, however, the signs and symptoms that aid in the differentiation of Cushing's syndrome, adrenogenitalism and the syndrome of large, pale ovaries are that in the first there is muscular weakness and pseudomasculinization and in the second there is increased strength and true virilism, and in the third there is hirsutism with marked femininity. The 17-ketosteroids in Cushing's disease may be normal or slightly increased.[24] Assays of 11-oxycorticoids are significant, being markedly elevated in Cushing's disease. On performance of the Thorn (ACTH) test[25] the circulating eosinophil count is of utmost value. In Cushing's disease or syndrome the fasting eosinophil count is usually below 100. If the count is much above this number, then the disorder is probably not Cushing's disease.

Treatment—Surgery is indicated when a markedly enlarged adrenal gland or adenoma is found on perirenal insufflation or by roentgenographic studies. Roentgen therapy to the pituitary gland has been followed by commendable improvement or temporary remission in some patients and should be undertaken par-

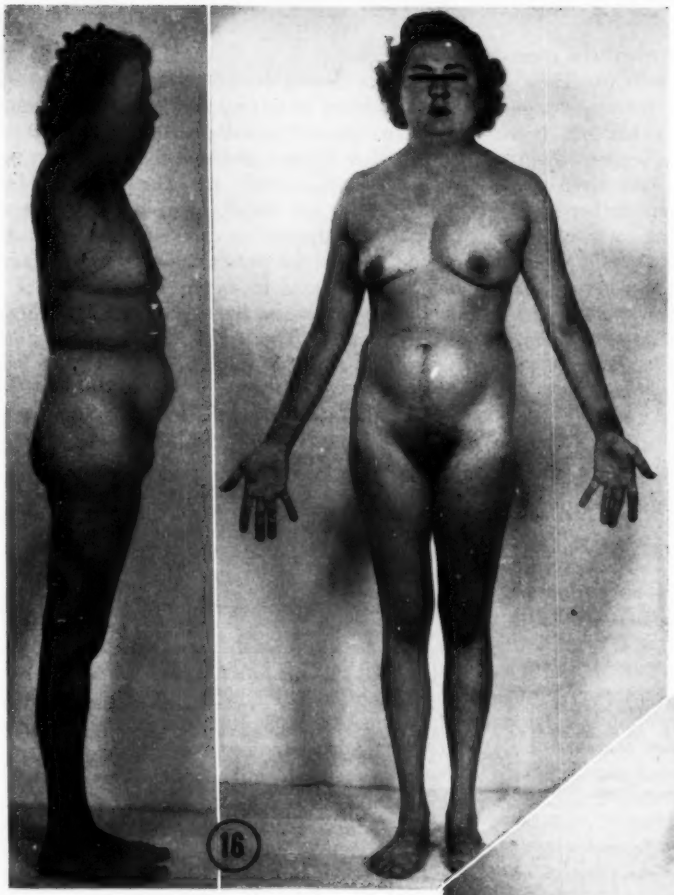


FIGURE 16. Cushing's disease in 23-year-old female. Note typical plethoric moon face and obesity confined to shoulders and neck sparing the extremities. This patient was only mildly hirsute. She had hypertension (200/110), decreased carbohydrate tolerance, resistance to insulin, mild osteoporosis of vertebrae. Urinary 17-ketosteroids averaged 49 mg. per 24 hours and 11-oxycorticoids 3.6 mg. per 24 hours (normal range 0.2 to 0.5 mg. per 24 hours).

FIGURE 17. Note striae which were purplish in color.

ticularly in those rare instances when the roentgenograms reveal an enlarged sella turcica.

Endocrine therapy—Estrogen therapy designed to depress pituitary activity has not been very successful. Progesterone has been used with some improvement. Androgens have given most beneficial results. It may seem rather paradoxical to administer androgens to a woman already hirsute but the symptoms of the disease are due to protein lack and testosterone has nitrogen-sparing properties. Testosterone propionate may be administered in doses of 25 mg. twice weekly or testosterone pellets may be implanted every four to six months.

IDIOPATHIC HIRSUTISM

Hirsutism in those cases where no endocrine or metabolic disturbance is found is for the present classified as "idiopathic hirsutism." It is felt that this is due to the patient's hair follicle sensitivity to intrinsic androgens. Ovulatory menstrual periods usually occur with regularity and sterility is not a problem. In occasional cases functional amenorrhea may be present. Hormonal assays are usually within the limits of normal. The therapy of this condition is experimental and for the present electrolysis is recommended for facial hirsutism and the use of a depilatory for excess hair growth on the body and extremities. The use of a fine pumice stone is also said to be of value as it breaks the hair off at the level of the skin. The use of an alcoholic solution of estrogens topically appears to retard the rate of hair growth somewhat.[26]

The alcoholic solution of estrogen used in this study was supplied as ESTINYL SOLUTION,® and the testosterone propionate as ORETON,® by Schering Corporation through the courtesy of Dr. Edward Henderson.

REFERENCES

1. STEIN, I. F. and LEVENTHAL, M. L.: Amenorrhea associated with bilateral polycystic ovaries. Am. J. Obst. & Gynec. 29:181, 1935.
2. STEIN, I. F. and COHEN, M. R.: Surgical treatment of bilateral polycystic ovaries—amenorrhea and sterility. Am. J. Obst. & Gynec. 38:165, 1939.
3. STEIN, I. F.: Bilateral polycystic ovaries. Am. J. Obst. & Gynec. 50:385, 1945.
4. STEIN, I. F., COHEN, M. R. and ELSON, R.: Results of bilateral ovarian wedge resection in 47 cases of sterility. Am. J. Obst. & Gynec. 58:267, 1949.
5. GEIST, S. H. and GAINES, J. A.: Diffuse luteinization of the ovaries associated with the masculinization syndrome. Am. J. Obst. & Gynec. 43:975, 1942.
6. CULINER, A. and SHIPPEL, S.: Virilism and theca cell hyperplasia of the ovary: A syndrome. J. Obst. & Gynec., Brit. Emp. 56:439, 1949.
7. MEAKER, S. R.: Ovarian resection for the relief of sterility. Fertility and Sterility 1:293, 1950.
8. GREENBLATT, R. B. and PUND, E. R.: The gonadotropins: A clinical and experimental study. South. M. J. 34:730, 1941.
9. GREENBLATT, R. B. and TORPIN, R.: The evaluation of the various gonadotropins. J. M. A. Alabama, June, 1940.
10. GREENBLATT, R. B.: Histologic changes in the ovary following gonadotropin administration. Am. J. Obst. & Gynec. 42:983, 1941.
11. INGERSOLL, F. M. and MCDERMOTT, W. V.: Bilateral polycystic ovaries, Stein-Leventhal syndrome. Am. J. Obst. & Gynec. 60:117, 1950.
12. NIEBURGS, H. E. and GREENBLATT, R. B.: The significance of specific estrogenic, progestogenic and androgenic smears in menstrual disorders and in pregnancy. South. M. J. 41:972, 1948.
13. "Abiotrophy of the ovary"—a term coined by Dr. E. R. Pund, Professor of Pathology, Medical College of Georgia, to denote poorly functioning ovaries histologically.
14. HAYMAKER, W. and ANDERSON, E.: The syndromes arising from hyperfunction of the adrenal cortex. Internat. Clin. 4:245, 1938.
15. WINTERSTEINER, O.: The Adrenogenital Syndrome, Glandular Physiology and Therapy. American Medical Association, Chicago, 1942.
16. MELICOW, M. M. and CAHILL, G. F.: Adrenal cortex in somatosexual disturbances in children. J. Clin. Endocrinol. 10:12, 1950.
17. NOVAK, E.: Gynecology and Female Endocrinology. Little, Brown and Co., Boston, 1941.
18. WILKINS, L.: A feminizing adrenal tumor causing gynecomastia in a boy of five years, contrasted with a virilizing tumor in a five year old girl. J. Clin. Endocrinol. 8:111, 1948.
19. CHANEY, R. H. and GREENBLATT, R. B.: The adrenogenital syndrome. J. M. A. Georgia 12:482, 1950.
20. ALLEN, W. M., HAYWARD, J. S. and PINTO, A.: Color test for dehydroisoandrosterone. J. Clin. Endocrinol. 10:54, 1950.
21. KEPLER, E. J. and LOCKE, W.: Chronic adrenal hyperfunction. In: Textbook of Endocrinology, edited by R. H. Williams. W. B. Saunders Co., Philadelphia, 1950.
22. MASON, H. L. and SPRAGUE, R. G.: Isolation of 17-hydroxycorticosterone from the urine in a case of Cushing's syndrome associated with severe diabetes mellitus. J. Biol. Chem. 175:451, 1948.
23. ALBRIGHT, F., PAKSON, W. and BLOOMBERG, E.: Cushing's syndrome interpreted as hyperadrenocorticism leading to hypergluconeogenesis: Results of treatment with testosterone propionate. J. Clin. Endocrinol. 1:375, 1941.
24. FORBES, A. P., CARROLL, E. L. and WHEELER, M. L.: A comparison of the 17-ketosteroid excretion of cases of Cushing's syndrome due to adrenal tumor with those due to hyperplasia (hyperfunction). (Abstr.) J. Clin. Endocrinol. 9:680, 1949.
25. THORN, G. W., FORSHAM, P. H., PRUNTY, F. T. G. and HILLS, A. G.: Test for adrenal cortical insufficiency; response to pituitary adrenocorticotropic hormone. J.A.M.A. 137:1005, 1948.
26. GREENBLATT, R. B.: Secondary sex characteristics. Contrasting cases of precocious puberty, Cushing's disease and sexual infantilism. Postgrad. Med. 1:223, 1947.

Diagnostic Clinic

Pathologic Physiology of Mitral Stenosis

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Interest in mitral stenosis has been aroused by recent attempts at surgical correction of the lesion. Such attempts can be better evaluated if the pathologic physiology of mitral stenosis is understood. A characteristic case is presented together with a discussion of diagnostic criteria and treatment.

The patient I will discuss is a 40 year old man with mitral stenosis. This patient was well until the age of 10 when he developed aching pains in his legs, which probably represented an attack of rheumatic fever, although we cannot be sure. After this he was again asymptomatic until January, 1944, when he was in the Navy. At this time he developed mild exertional dyspnea. He was examined and found to have a heart murmur and was discharged from the Navy.

He was first admitted to the hospital in November, 1944, with a history of severe hemoptysis a week prior to admission. Examination at that time revealed the typical murmur of mitral stenosis, but there was no evidence of congestive heart failure and the heart was not enlarged either to physical examination or by roentgenographic examination. The electrocardiogram showed no evidence of right axis deviation.

After leaving the hospital he was able to work for a year, but following this he had increasing dyspnea and finally was unable to maintain his vocation.

In March, 1946, he had a severe hemoptysis and was again readmitted to the hospital. At that time a right pleural effusion was found, and râles were found at the bases of both lungs. There was no enlargement of the liver and no edema. The heart was now enlarged and showed the same murmur, and the x-ray showed a typical mitral contour of the heart. The electrocardiogram revealed a right strain pattern.

The patient was then again discharged. He continued to be dyspneic and was readmitted in March, 1947, because of severe hemoptysis. At this time there was no evidence of right heart failure, and the remainder of the findings were essentially the same.

In January, 1948, he developed severe dyspnea, orthopnea and hemoptysis, and was again readmitted to the hospital. Examination this time showed a small right pleural effusion. The liver was slightly enlarged, but there was no edema and the cardiac findings were essentially as before.

Following discharge he continued to be dyspneic on slight exertion and to have frequent hemoptyses. He was placed on digitalis and a low salt diet.

He was readmitted again in April, 1949, because of dyspnea and hemoptysis. The findings at that time were essentially unchanged, but while in the hospital he developed a thrombophlebitis which required bilateral ligation of the superficial femoral veins.

His final admission was in August, 1950, be-

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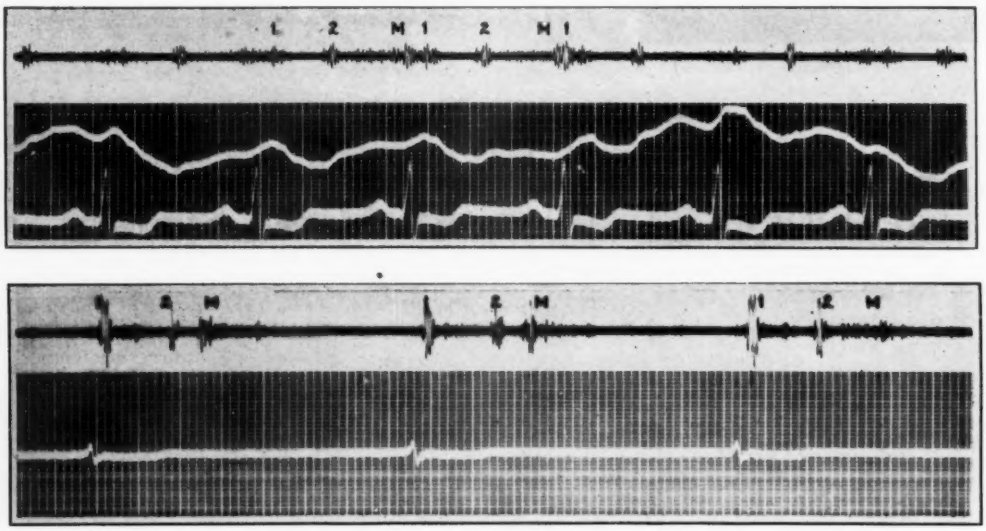

FIGURE 1. Phonocardiogram (top), showing first and second heart sounds and murmur. The murmur is most marked immediately before the first heart sound, the so-called presystolic murmur. (Bottom) Tracing of patient showing auricular fibrillation, mitral stenosis and typical mid-diastolic murmur.

cause of recurrent hemoptyses and pain in the left anterior chest. At this time there was moderate distention of the neck veins, râles in both lower lungs, and a pleural pericardial friction rub. There was no enlargement of the liver and no edema. The patient was thought possibly to have a pulmonary or splenic infarct, although an absolute diagnosis could not be made.

In January, 1948, while in the hospital he had cardiac catheterization studies, and at that time his pulmonary artery pressure was 68/31 mm. of mercury, which is approximately three times the normal value. His right auricular pressure was normal.

On examination of the heart of this particular patient, palpation revealed the apex impulse to be about 4 cm. outside the midclavicular line in the fifth midinterspace. There was a thrust over the pulmonary artery. Percussion revealed moderate enlargement with a bulge in the third interspace. Auscultation revealed a typical presystolic murmur at the apex, the typical murmur of mitral stenosis, and there was a markedly accentuated pulmonic second sound.

Figure 1 is a phonocardiogram. The top one is the phonocardiogram of the patient I am presenting today. As I mentioned before, he showed a typical presystolic murmur. You notice that the murmur is most marked immediately before the first heart sound, the so-called presystolic murmur. However, if one examines the tracing fairly carefully, one finds that there are a few vibrations early in diastole, so really it is a combination of a mid-diastolic and presystolic murmur and this is usually the case if the phonocardiogram is carefully studied.

You also notice there is absolutely no murmur in systole, so here we have a pure mitral diastolic murmur without any systolic murmur whatsoever. This would presumably be indicative of pure mitral stenosis.

For comparison I have included the tracing of a patient with auricular fibrillation, mitral stenosis, and a typical mid-diastolic murmur. You all remember that when auricular fibrillation ensues the murmur is no longer presystolic in character because the auricle no longer is effective in pushing blood through the mitral valve, and we usually have a mid-diastolic murmur instead of a presystolic murmur. This is a very beautiful example of that.

This is called a mid-diastolic murmur, but as I mentioned, it actually occurs rather early in diastole. However, the characteristic feature is that there is a pause between the second heart sound and the onset of the murmur. The silent

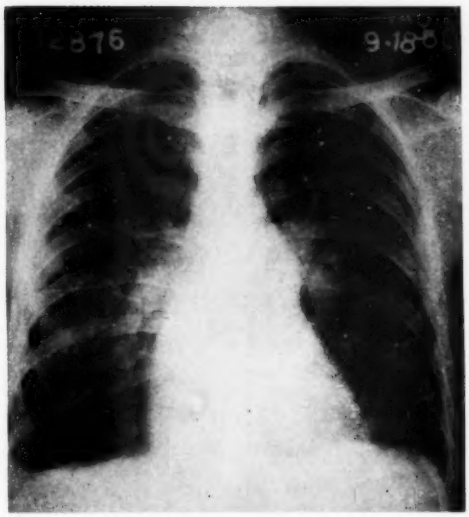

FIGURE 2. Posteroanterior roentgenogram, showing typical mitral contour of the heart. There is a prominent bulge in the region of the pulmonary artery and the left border is straight.

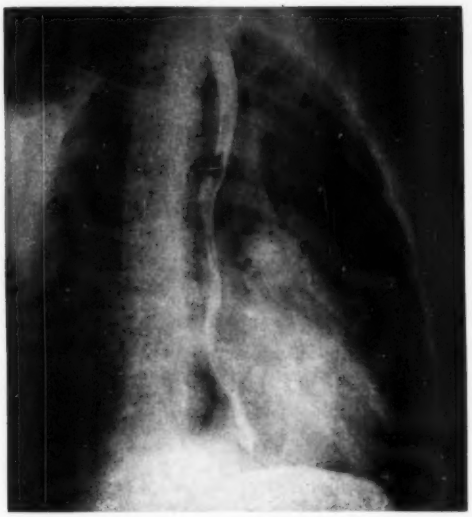

FIGURE 3. A right anterior oblique view of the same patient shown in Figure 2. There is typical displacement of the esophagus by the left auricle, and bulging in the conus area, which represents enlargement or dilatation of the pulmonary conus.

period between the second heart sound and the onset of the murmur represents the isometric period of diastole when there is no flow of blood from the auricle to the ventricle.

You also notice the accentuation of the sound at the very beginning of the murmur—actually it forms a real sound here—and that sound is sometimes called the opening snap of the mitral valve.

Figure 2 is the roentgenogram of the patient I am presenting, the posteroanterior view of the chest, and you notice the typical mitral contour of the heart. The heart tends to be somewhat round in contour; it is not at all like the boot-shaped contour of left ventricular enlargement. There is a prominent bulge in the region of the pulmonary artery and the left border is straight.

The lungs reveal some increase in markings, and if you look at the roentgenogram you see some little tiny nodular densities out in the periphery of the lung field consequent to the chronic passive congestion.

A right anterior oblique view of the same patient is shown in Figure 3. You will notice the typical displacement of the esophagus by the left auricle. Also you will notice the bulging in this area, which represents enlargement or dilatation of the pulmonary conus.

Figure 4 is the electrocardiogram of the patient I presented and shows a typical example of so-called right strain pattern. Limb leads I, II and III are the standard leads that we always use. V-1, V-2, V-3, V-4, V-5 and V-6 are unipolar precordial leads, the V-1, of course, being to the right of the sternum, V-4 in the region of the fifth interspace midclavicular line, and V-2 and V-3 in between.

There are typical findings of right axis deviation, a deep S-wave in lead I and a high R-wave in lead III. In addition, another characteristic feature in the limb leads of right strain pattern is the inverted T-waves in leads II and III and the depression of the ST segments in these particular leads. That does not imply any coronary disease but merely right heart hypertrophy, as does the remainder of the pattern.

In the precordial leads we find the classic pattern. The R-wave in V-1 is approximately the same height as the R-wave in V-4, V-5 and V-6. The T-wave is inverted in V-1 and upright in the remainder of the leads; also, there is some delay of the peak of the R-wave in V-1, so that we have the characteristic findings of a right strain pattern, both in the limb leads and in the precordial leads.

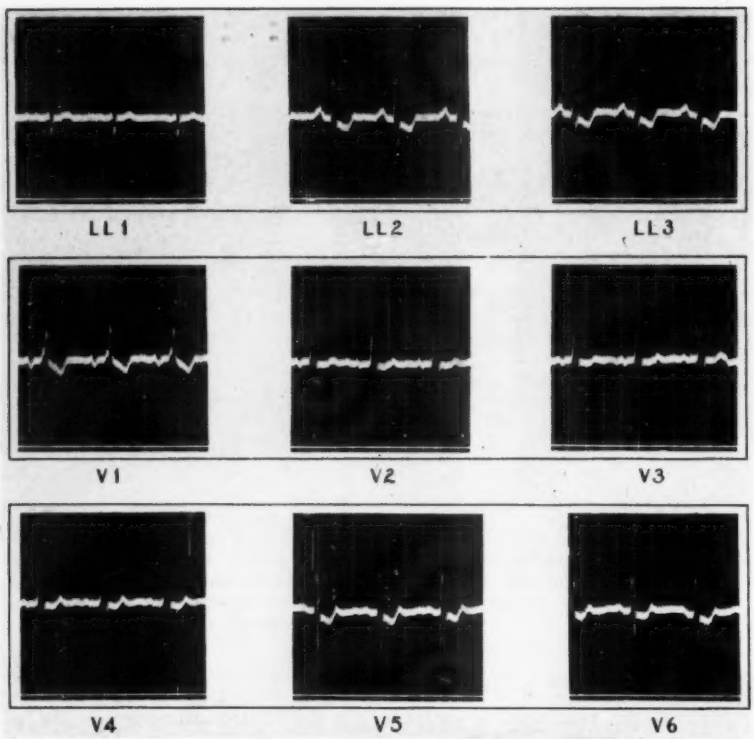

FIGURE 4. Electrocardiogram of the same patient, showing a typical example of right strain pattern.

I presented this patient today because he shows the classic history, physical findings, roentgenographic findings, and electrocardiographic findings of a patient with severe mitral stenosis. You will note that the patient was incapacitated by dyspnea and hemoptysis over a period of many years, six years to be exact. This is rather characteristic of mitral stenosis. It leads to long-term incapacitation of the patient as contrasted to left ventricular failure, which usually runs a more rapid course. Patients with mitral stenosis may be chronic invalids for many, many years.

The other classic feature is the recurrent hemoptysis which is so characteristic of this particular disease.

I thought you might be interested in hearing a discussion of mitral stenosis today because of the interest that has been aroused in this particular subject by recent attempts at surgical correction of the lesion, and I thought perhaps you could better evaluate the attempts that are being made if you understood something of the pathologic physiology of mitral stenosis. I am going to attempt to give you my opinion on that particular subject.

FIRST, of course, we have to consider the pathology of mitral stenosis. For example, in a picture of the mitral valve taken from the open left atrium looking down on the mitral valve, the mitral valve is so tremendously narrowed that it is a little difficult to make out. The left atrium is somewhat dilated, and down at the base of the left atrium there is a very narrowed valve—that is all there is to the opening, just a slit.

In a case of this type it is perfectly easy to understand how there is tremendous difficulty in blood flow through the valve. The tremendous narrowing that is present markedly interferes with flow through the valve. All patients with mitral stenosis do not have as simple a situation as this. Some of the patients will have a combination of mitral stenosis and insuffi-

ciency, and the valve, while narrowed, will admit, say, one finger. The chorda tendineae are shortened and we have physiologically a combination of mitral stenosis and regurgitation, which may produce as deleterious effects on the patient as pure mitral stenosis alone. I do not want to leave you with the impression that all patients with mitral disease have a valve which looks like this at the time of death. Some do not. This is tremendously important when considering these patients for mitral valve surgery.

What effect does this narrowing of the mitral orifice have on the circulation? In the first place, it produces the characteristic murmur, and apparently the murmur can occur before any hemodynamic effects are detectable; in other words, one may hear the characteristic murmur of mitral stenosis before one has any symptoms on the part of the patient, before any alteration in pulmonary function occurs, such as reduction in vital capacity, and before any changes in the pressures in the pulmonary system occur.

If the stenosis becomes more severe, certain changes occur in the pulmonary circulation, and probably the first change is a rise in left auricular pressure. We are unable to measure this directly at the moment, but we arrive at this by deduction. There is usually associated with this some decrease in the cardiac output, that is, in the amount of blood that is being pumped by the heart.

TABLE 1

RESULTS OF STENOSIS OF THE MITRAL VALVE

1. Production of a characteristic murmur
2. When stenosis is severe there is a rise in left auricular pressure with usually a decrease in cardiac output

   Formula for flow through narrow orifice

   $$Q = A\sqrt{2gh}$$

3. Effect of mitral regurgitation

The rather complicated formula in Table 1 is not intended to impress you but to give you an idea of some of the factors that control flow through a narrowed valve of this kind. This is Toricelli's law. Q would be the amount of blood going through the valve, A would be the area of the valve, h the venous pressure in the left auricle, and g represents gravity. This formula does not become operable until the valve becomes extremely narrowed, and then as the area narrows further either the quantity of blood passing through the valve must decrease, as you can see, or the pressure must increase. The pressure has to increase as the square to increase the quantity, which makes a very difficult situation. So we have these three factors involved: (1) the flow through the valve, (2) the area of the valve, and (3) the pressure forcing the blood through the valve.

This would be complicated enough, but in addition, in most cases of mitral disease, we have an associated mitral regurgitation of a variable degree which adds confusion to the issue because, of course, the blood that regurgitates through the valve during systole has to flow back through the valve during diastole, so it accentuates the functional effect of the stenosis.

TABLE 2

EFFECT OF CHRONIC PULMONARY VENOUS HYPERTENSION

1. Dilatation of left auricle
   (a) auricular fibrillation
   (b) thrombus formation
2. Chronic passive congestion of the lungs
   (a) exertional dyspnea
   (b) cough
   (c) hemoptysis
3. Pulmonary arterial hypertension

It is our feeling that the elevated venous pressure in the left auricle is the factor causing the harm to these particular patients (Table 2). Before they have this they probably behave as relatively normal people, but this elevated pressure causes a number of effects, particularly on the left auricle and on the pulmonary circulation, which cause the patient's symptoms.

We are all familiar with the dilatation of the left auricle in mitral disease, and in part, at least, this is related to the elevated pressure in the left auricle, although there probably are other factors involved. For instance, occasional patients with severe mitral stenosis will have relatively little dilatation of the left auricle; others will have enormous dilatation. Particularly in patients with marked mitral regurgitation the dilatation of the left auricle may be immense, so that there is no real direct correlation between the severity of the mitral stenosis and the size of the left auricle, although in general

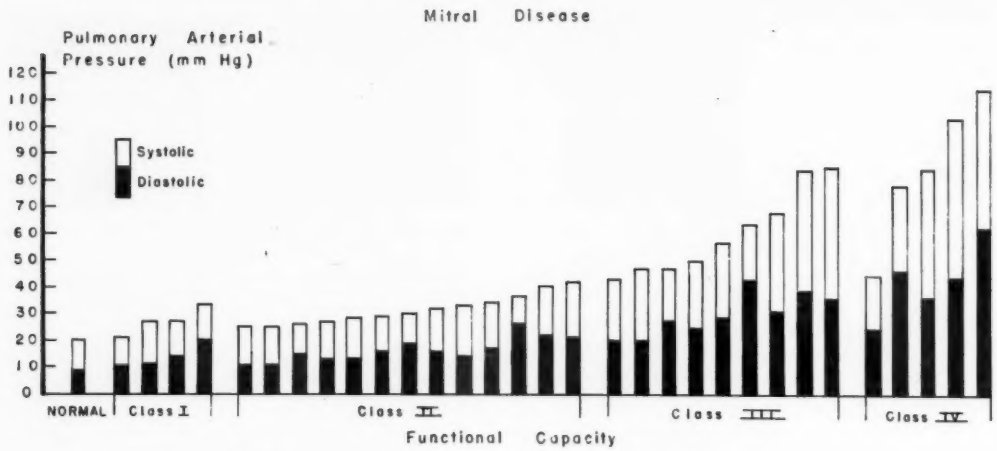

FIGURE 5. Pressure readings from patients with mitral disease.

From: BORDEN, EBERT, WILSON and WELLS: Pulmonary hypertension in heart disease. New England J. Med. 242:529-534 (April 6) 1950.

most patients with symptomatic mitral disease will have some dilatation of the left auricle.

This dilatation of the left auricle produces—or tends to predispose to—auricular fibrillation. The onset of auricular fibrillation in itself accentuates the difficulty with regard to blood flowing through the valve. If the patient fibrillates rapidly, the diastolic period shortens so there is less time for the blood to flow through the valve; hence when we have the onset of auricular fibrillation in the patient with mitral stenosis, there is usually marked accentuation of the patient's symptoms, and slowing of the fibrillation with digitalis or conversion to normal rhythm with quinidine will usually cause a marked improvement in the patient's symptoms. Not only that, but dilatation of the left auricle and oftentimes superimposed auricular fibrillation predispose to thrombus formation in the left auricle. This thrombus formation may occur in the auricular appendage alone or may actually occur in the atrium itself, and as you all know, the great danger of thrombus formation is the breaking off of bits and pieces to form emboli. Many patients with mitral disease are incapacitated by these systemic emboli either to the brain, to one of the major arteries of the extremities, to the superior mesenteric artery, to the spleen or to the kidney. These form a very major feature of the symptomatology of certain patients with mitral disease, particularly if they have auricular fibrillation.

In addition, the elevation in venous pressure produces congestive changes in the lungs and we have the characteristic symptoms of exertional dyspnea, cough, and hemoptysis. You will note that at this stage of the disease the symptoms are really pulmonary in origin, so many of these patients are diagnosed as having pulmonary disease rather than heart disease. Because of the hemoptysis and cough they may be diagnosed as having bronchiectasis or chronic bronchitis and the mitral disease may be missed completely.

In a sense this is not true heart failure because it is not myocardial failure; the myocardium is not failing at this point. It is actually a hemodynamic disturbance in the lung as a result of difficulty in flow through this narrowed valve.

THE other condition that develops is severe hypertension in the pulmonary artery, and this particular feature is rather complex because the degree of hypertension developed in the pulmonary arteries seems to be disproportionate to what one might expect; the pressure in the pulmonary artery may approach that in the systemic circulation. You notice that in the case I showed today the pressure was 68/31 mm. of mercury, but in some patients the pressure may go as high as 100/60. We do not think that the rise in pressure in the pulmonary artery is due

simply to back pressure from elevated venous pressure in the left auricle. There is often a factor of increased vascular resistance in the lung itself.

Figure 5 is just a record of some pressure readings from patients with mitral disease and gives an idea of the degree of pulmonary arterial hypertension which exists. These patients are divided into class 1, without symptoms; class 2, symptoms on moderate exertion; class 3, symptoms on slight exertion, and class 4, patients who have symptoms at rest. The normal pressure is about 20/10 mm. of mercury. The patients in classes 1 and 2 have relatively slight pulmonary artery hypertension, whereas the patients in classes 3 and 4 have fairly severe pulmonary arterial hypertension.

To summarize it a little better, the normal figure for pressure in the pulmonary artery is 20/9 mm. of mercury; the value for classes 1 and 2, those with rather mild symptoms, is 30/16 mm. of mercury. The severe hypertension which tends to be present in the patients with dyspnea on slight exertion or dyspnea at rest, 69/34 mm. of mercury, is almost three and a half times the normal pressure in the pulmonary arteries. You also note that the cardiac output or the amount of blood pumped by the heart tends to be lower in those patients with severe mitral stenosis. So that now, through cardiac catheterization, we have objective evidence that in patients with severe mitral disease there is a very marked increase in the pressure in the pulmonary arteries.

What effect does this elevation in blood pressure in the pulmonary artery have on the circulation? It accounts for the accentuated pulmonic second sound which is so characteristic of mitral stenosis; it accounts for the Graham Steell murmur—that is, the early diastolic murmur resembling that of aortic insufficiency heard along the left sternal border which is due to pulmonary regurgitation. It produces dilatation of the pulmonary artery, it produces hypertrophy of the right ventricle, and eventually produces right heart failure. Actually, many of the manifestations that we consider classic for mitral stenosis are in reality manifestations of pulmonary hypertension, that is, the dilatation of the pulmonary artery, the marked hypertrophy of the right ventricle, and the right heart failure which eventually ensues (Table 3).

TABLE 3

EFFECT OF PULMONARY ARTERIAL HYPERTENSION

1. Accentuated pulmonic second sound and Graham Steell murmur
2. Dilatation of pulmonary artery
3. Hypertrophy of right ventricle
4. Right heart failure

I want to say a word or two about treatment. It is apparent that in the earlier stages of mitral stenosis when the patient has the symptoms of dyspnea, hemoptysis and cough, we are not dealing with myocardial failure as I mentioned before, but with mechanical obstruction to the blood flow through the mitral valve. If the patient has a normal sinus rhythm it is obvious that digitalis is going to have relatively little effect, because the myocardium is not at fault in this particular stage of the disease. It is for this reason that surgeons are working constantly on methods of enlarging the orifice of the mitral valve by some surgical procedure. It seems logical, when seeing a valve such as I discussed earlier, to try to enlarge this opening so the blood can again flow through in a normal manner, thus improving the hemodynamic changes in the lungs which produce these severe symptoms.

One of the problems facing the surgeon under these circumstances is the fact that the patient may have mitral regurgitation to begin with or that the operation itself may cause mitral regurgitation. This is the problem which has caused surgery on the mitral valve to be delayed and is causing difficulty at the present time.

From the medical standpoint there are things we can do for these patients if they develop auricular fibrillation. Digitalis is of the utmost importance because, as I mentioned before, the rapid rate shortens the period of diastole and interferes with the flow through the valve, and slowing the rate will improve the patient's symptomatology. Not only that, but if the patient has only fibrillated for a short time, frequently we can convert him to a normal sinus rhythm temporarily with quinidine. So there are definite things we can do if these patients develop auricular fibrillation.

Also, if they develop right heart failure we have the usual treatment for this particular disorder: digitalis, low salt diet and diuretics.

Finally, I would like to mention a word or

two about the treatment of embolic phenomena in mitral stenosis. This is of tremendous importance to certain patients. Some patients may have relatively few symptoms from their disease and yet be cursed by repeated systemic emboli with hemiplegias, with loss of a leg due to occlusion of one of the major arteries to the extremity or with recurrent attacks of pain due to splenic and renal infarcts. In these patients we can give help by the use of the modern types of anticoagulants, heparin and DICUMAROL,® and indeed it may be indicated in some of these patients to keep them permanently on dicumarol.

Another advance that is being investigated surgically is the matter of ligation or removal of the auricular appendage of the left auricle, because here it is that most of these thrombi originate. I think this is still in the experimental stage, but we have some hope that it will offer relief for this type of patient.

THE GOLDEN LEAF

Anatomic Study by Pavel Tchelitchew

(Reproduced, courtesy Durlacher Brothers)

Pathology in General Surgery*

Postgraduate Medicine *here presents the second part of a selection of color plates and descriptive text from the book, "Pathology in General Surgery." The first group of reproductions was published in the May issue. Illustrations and text are reproduced with the permission of The University of Chicago Press.*

Carcinoma of the Lung

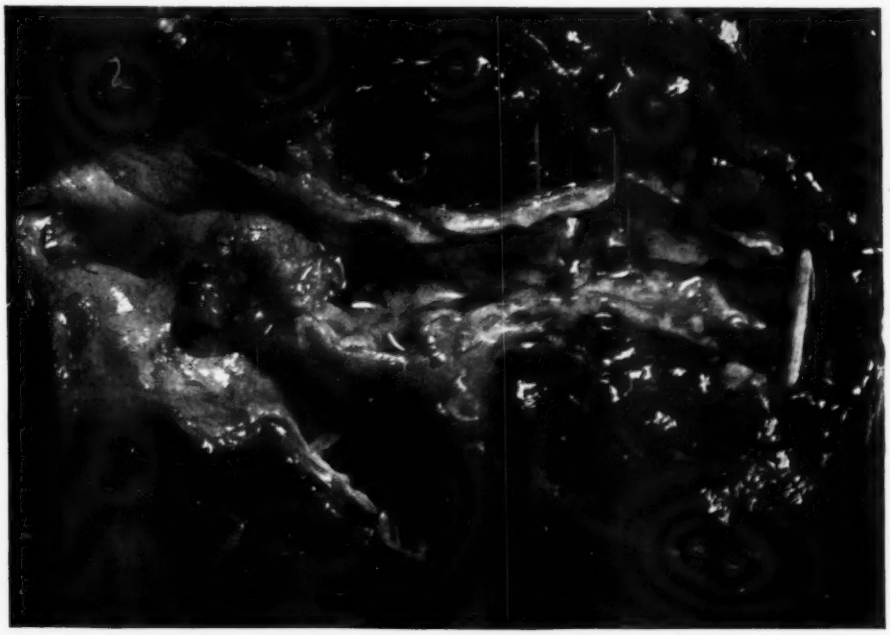

Plate 163.—Carcinoma at the bifurcation of the left stem bronchus, causing obstruction of the upper lobe bronchus, with bronchiectasis, atelectasis, and abscess formation. For 1 year this fifty-three-year-old man had complained of cough, productive of blood-streaked sputum for 3 months.

*Pathology in General Surgery. By Paul W. Schafer, M.D., Professor of Surgery and Chairman of the Department, University of Kansas School of Medicine. 581 pages, with 495 illustrations, 368 in color. 1950, The University of Chicago Press, Chicago. $17.50.

CARCINOMA OF THE LUNG

The rapid development of intrathoracic surgery during the last 15 years has stimulated much interest in carcinoma of the lung. In the past few years several articles have appeared reporting an actual increase in the incidence of this disease, and this may be true. However, it seems more likely that this increase is more apparent than real and probably relates itself to a more active quest for the disease. In general, carcinoma of the lung is six times as common in males as in females, being nearly as common as carcinoma of the stomach in males. The condition is observed in the usual cancer age groups, occurring most frequently in the sixth decade of life. Little is known of its etiology, though many possible factors have been considered. Most of these are presumed to cause a chronic irritation of the respiratory membranes, and they include atmospheric pollution by tobacco smoke, exhaust gases, coal-tar products, and related substances, as well as the chronic inflammatory changes associated with lung abscess, tuberculosis, silicosis, bronchiectasis and chronic bronchitis. Little evidence exists to incriminate any of the above causative factors.

Three-fourths of all lung carcinomas are located either in or adjacent to the stem bronchi, their presence usually being indicated by cough. The cough associated with lung carcinoma is in no way characteristic, and, since many persons in the usual age group for these tumors have a chronic cough, it is often not considered of significance either by the patient or by his physician. Usually the patient is aware that the cough is different from any which he has experienced before in that it is more persistent, paroxysmal, or may be productive of a blood-streaked, mucoid, or mucopurulent sputum.

Carcinoma of the lung differs sharply from carcinoma of other organs in that it commonly produces pain relatively early in its course. The pain is not pleuritic in character but is rather a constant, dull, aching or burning distress situated deep in the chest. The patient is often able subjectively to localize the area in which the tumor mass is subsequently demonstrated by roentgenographic examination. Hemoptysis is a relatively late finding, and even then it is observed in less than half these patients. Usually it consists only of blood-streaking of the sputum, though occasionally gross bleeding occurs. As the tumor progressively enlarges and occludes one or more major bronchial divisions, dyspnea is likely to become a prominent symptom. As with other carcinomas, late in the course of the disease loss of weight and strength occurs.

If not discovered until after they have produced symptoms, the peripheral carcinomas are prone to have invaded the visceral pleura with the development of a bloody pleural effusion in which tumor cells may be demonstrated. Such extensions are likely to produce pleuritic pain; and, if the tumor extends through an area of visceroparietal pleural symphysis, adjacent structures may be invaded. When a tumor of this type is located in the apex, involvement of the ribs, the brachial plexus, the axillary vessels, and the sympathetic trunk gives rise to the clinical syndrome described by Pancoast. This consists of pain in the shoulder, impairment of circulation to the upper extremity, and an ipsolateral Horner's syndrome. Many times the first symptoms of a peripherally located lung carcinoma are referable to remote metastases in the brain or skeleton. The appearance of a cervical lymph node metastasis may also direct attention to a silent primary carcinoma of the lung.

The bronchial adenoma is not ordinarily classified as a carcinoma, though almost all students of this disease recognize that this tumor directly invades the surrounding bronchial wall and lung parenchyma and metastasizes not only to regional hilar lymph nodes but also to remote organs. Characteristically it is observed with greatest frequency in the third and fourth decades and in about equal incidence in the two sexes. It usually causes cough and hemoptysis. Often it is subjected to bronchoscopic fulguration, following which it almost invariably recurs. If not resected, this tumor progressively enlarges within the stem bronchus and eventually causes obstruction of the lung with secondary atelectasis and infection. Often after many years the tumor extends upward to involve the carina and to obstruct the opposite stem bronchus. Thus, late in its course, increasing dyspnea develops, the patient often succumbing during a bout of asphyxia. In all probability the bronchial adenoma should be regarded as a carcinoma of slow rate of growth with a tendency for the late development of metastases.

Grossly the typical hilar carcinoma of the lung consists of a hard, irregular mass varying from a few to many centimeters in diameter, involving a considerable portion of the wall of either the stem bronchus or one of its primary branches, and extending for a variable distance into surrounding lung parenchyma. The tumor presents a relatively homogenous, whitish-gray cut surface without sharp demarcation from the adjacent lung. The nodular endobronchial surface of the tumor is invariably ulcerated. Bronchial obstruction, due either to circumferential narrowing of the lumen or to polypoid projection of the tumor into the airway, results in atelectasis of a lobe or of the entire lung, depending on the location of the obstruction. Secondary inflammatory changes in the obstructed lung include bronchietasis, lung abscess, and pneumonitis.

Regional Enteritis

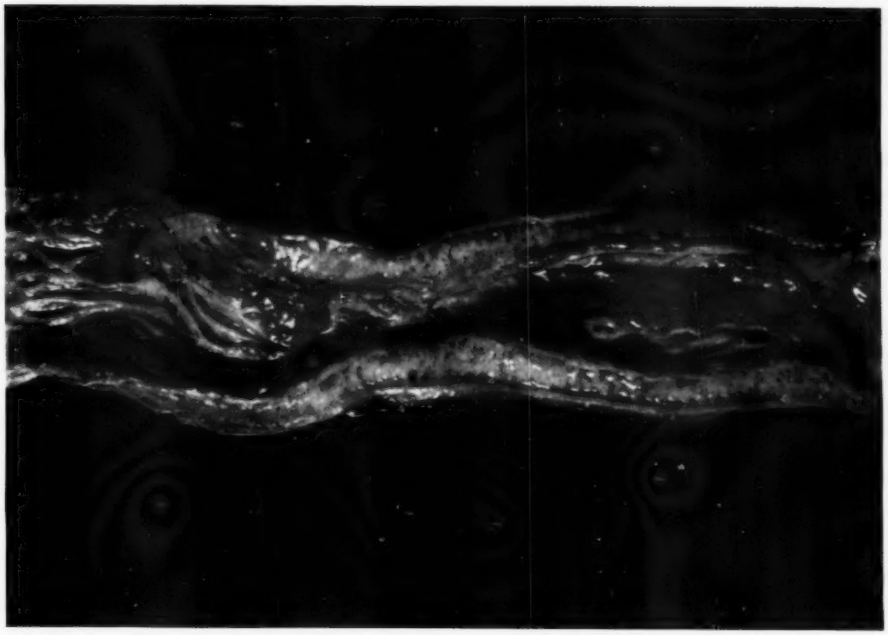

Plate 328.—Segment of ileum involved by regional enteritis, resected from a thirty-seven-year-old man, who for 1 year had been chronically ill with intra-abdominal abscesses and fistulas of the abdominal wall. A communication between the terminal ileum and sigmoid was found at operation. Prompt recovery followed resection of all diseased areas of the bowel.

Pancreatic Fat Necrosis

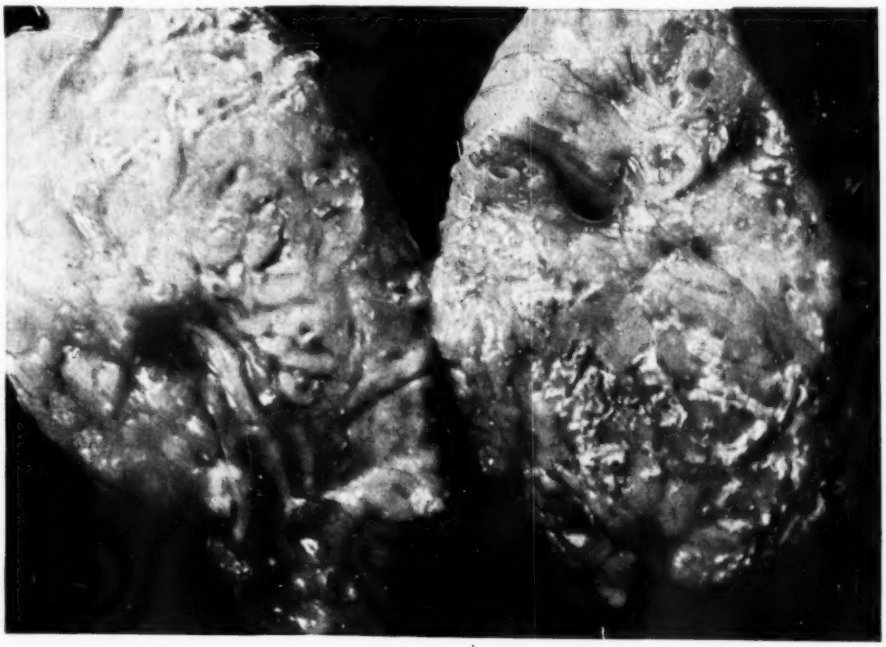

Plate 421.—Extensive irregular areas of opacity, seen on examination of the cut surface of the pancreas. This change results from the saponification of fatty acids liberated from normal neutral fat by the action of pancreatic lipase, which escapes into the tissues during pancreatitis.

REGIONAL ENTERITIS

Regional enteritis was first described as a pathologic and clinical entity by Crohn, Ginzburg and Oppenheimer in 1932. Previous to this time this condition was usually classified under the general title of "benign granuloma," a group which includes several inflammatory diseases not known to be due to infection by a specific organism. Undoubtedly many cases were felt to be tuberculous or neoplastic in origin because of the close clinical and gross pathologic similarity of regional ileitis to these conditions.

This disease is characterized by a destructive, scarring inflammation which involves the wall of the small intestine, its mesentery and regional lymph nodes. As originally described, this process was thought to involve only the terminal few inches of the ileum; yet, as more cases have been studied, it has become apparent that the disease may affect long segments of the ileum in direct continuity and may be found in separate multiple foci throughout the ileum and jejunum, the bowel intervening between areas of involvement remaining completely normal. In addition it is now known that the disease may spread across the ileocecal valve to involve the cecum, appendix and extensive areas of the colon. Its clinical manifestations and gross and microscopic pathology are well documented; some variance of opinion exists as to its best method of treatment; and practically nothing is known of its etiology.

This is the most common severe chronic inflammatory disease of the jejunum and ileum of people residing in this country. Some idea of its frequency can be obtained from the fact that, within less than 7 years after its original description, the medical literature contained reports of 600 patients with this disease who had been subjected to operation. In 1945 Crohn reported on his personal study of 164 cases. In this hemisphere climate seems to be a factor of importance, since the disease is uncommon in the states and countries bordering the Gulf of Mexico and the Caribbean Sea. Negroes seem to be affected less frequently than are whites yet this may not be of fundamental importance. The sexes are represented about equally in most reports. Though the disease has been encountered in almost all age groups, the average age of onset of symptoms is between 25 and 30 years.

In general the clinical course is not unlike that of chronic nonspecific ulcerative colitis; indeed, in many respects these two diseases are alike. Diarrhea, fever, lower abdominal distress, loss of weight, and anemia are the prominent clinical features. Of these the most constant is diarrhea, the patient usually having two to five stools a day. However, in late stages of the disease when stenosis becomes marked, constipation or frank intestinal obstruction is not an uncommon complication. The stool is usually semisolid or mushy in character with considerable mucus and blood-streaking. Not infrequently fistulas and abscesses form in the perianal region, although this complication is more often seen in chronic nonspecific ulcerative colitis than in regional enteritis. Nausea and vomiting are encountered only at times of acute exacerbation or late in the stenotic phase of the disease, at which time they are associated with cramping lower abdominal pain, visible peristalsis, and the typical x-ray appearance of small bowel obstruction. Ordinarily the abdominal distress or pain is either distributed generally over the lower abdomen or is localized to the right lower quadrant. It is particularly likely to be associated with or relieved by defecation. When the disease process involves the sigmoid colon with the formation of an ileocolic fistula in this area, these symptoms and signs may be localized more to the left than to the right side of the lower abdomen.

Usually the general aspects of the clinical picture, such as fever, weakness, and loss of weight, are severe and tend to progress without spontaneous remission. Anemia occurs in the later stages of the disease. The stools almost always contain occult blood, even though gross blood-streaking is not evident. Sometimes a case is encountered in which all the above findings are absent or present in such a mild degree that the disease is demonstrated by x-ray examination, much to the surprise of the clinician.

CHRONIC PANCREATITIS

Chronic pancreatitis has assumed considerable significance for the surgeon, as he is called upon more and more frequently to differentiate it from carcinoma. Also some measure of relief now may be offered to those few patients who suffer persistent severe pain as the result of this condition. In most instances chronic pancreatitis is not associated with clinical symptoms and is encountered incidentally during abdominal exploration. Occasionally a history of prior acute pancreatitis may be elicited, and often there is associated disease of the biliary tract. When studied from the standpoint of pathogenesis, it is immediately apparent that this condition results from a variety of causes. These may be roughly classified under three headings: first, the deleterious action of various endogenous and exogenous toxins; second, the prior existence of bouts of severity; and third, the presence of pancreatic duct obstruction, caused either by appropriately situated tumors, stones, or sclerosing inflammatory processes. Either part or all of the organ may be affected, though usually the process is extensive.

An as yet undetermined, but probably small, percentage of these patients has symptoms referable to the inadequate production of endocrine

and exocrine secretions of the pancreas. Interference with insulin formation as a result of destruction of islet tissue gives rise to a mild diabetes, whereas extensive destruction of acinar tissue results in impairment of pancreatic juice secretion. Careful study of material aspirated from the duodenum under such circumstances reveals a substantial reduction in, or the frank absence of, pancreatic ferments. This may or may not be associated with clinical evidence of impaired fat digestion as determined either by quantitative estimation of unchanged fat present in stools after a measured test meal, or by the clinical finding of steatorrhea, the stools under such conditions being frequent, bulky and frothy.

The most distressing clinical manifestation of this disease, which fortunately is not common, is the occurrence of varying degrees of upper abdominal pain. This distress may be mild and intermittent in character but at times is extremely severe and persistent, often radiating through to the upper lumbar region. Such patients may require morphine to obtain even incomplete relief, and thus are prone to develop narcotic addiction. Few of these patients are able to remain gainfully occupied, and some are actually reduced to an invalid status. Pain seems to be related to increased tension within obstructed radicles of the duct system. Such obstruction may be caused either by inflammatory strictures or by incarceration of pancreatic calculi.

Of some value in establishing an accurate diagnosis of this condition is the use of scout films of the upper abdominal area. A few patients with this disease can be demonstrated to have irregular areas of increased density in the region of the pancreas; indeed, in some cases the general contours of the organ may be imperfectly outlined by the distribution of the calcific masses. These radiographic densities may be produced either by calcium deposition within the parenchyma of the gland itself or by the presence of numerous pancreatic calculi within the duct radicles. No sharp correlation exists between the radiographic demonstration of these calcific deposits and the character and severity of the patient's clinical symptomatology.

Most confusing is the occasional occurrence of an otherwise asymptomatic chronic pancreatitis, producing first evidence of its existence as a result of external compression of the intrapancreatic portion of the common bile duct. These patients have painless, obstructive jaundice and are clinically suspected of having obstruction due to carcinoma. This misinterpretation may not be clarified even at the time of exploratory operation, since, under such circumstances, the pancreas will be as firm and as nodular as if a carcinoma were present. Occasionally resection has been carried out on the basis of an incorrect diagnosis of carcinoma, the true state of affairs being discovered only on microscopic examination of the resected material. Equally confusing in this connection is the occurrence of extensive atrophy and sclerosis of the body and tail of the pancreas secondary to pancreatic duct occlusion as the result of a carcinoma situated deep within the head of the organ. Such a situation may be correctly evaluated at the time of exploration only by the most careful dissection and biopsy. Chronic pancreatitis is associated with varying degrees of fat necrosis in the pancreas and in the surrounding adipose tissues, particularly in the root of the mesentery.

Case Report

Dissecting Aneurysm Treated Successfully by Sympathectomy

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Willius and Cragg[1] have listed the following as reasons for failure to make the antemortem diagnosis of dissecting aneurysm: (1) relative infrequency of the condition, (2) absence of a characteristic syndrome and (3) limitation of special diagnostic adjuncts.

I wish to present a case which meets the known criteria for antemortem diagnosis of dissecting aneurysm of the thoracic aorta. The patient has since survived the rigors of a two-stage sympathectomy and at present is enjoying good health.

CASE REPORT

M. G., a 26 year old white woman, was first seen in 1946, complaining only of fatigue. She had had scarlet fever at the age of 3, nephritis with gross hematuria at 19, and a cesarean operation following mild eclampsia at the age of 24. There was no family history of hypertension, and both parents are living and well.

Physical examination revealed a well developed and well nourished woman with a blood pressure of 230 systolic, 160 diastolic. The apex beat of the heart was found to be in the left midclavicular line. The aortic second sound was much louder than the pulmonic second sound. No murmurs were audible. Good cardiac reserve was present. Femoral pulsations were pronounced; the blood pressure in both legs was 260/170. Funduscopic examination revealed the media to be clear and the disks flat. No hemorrhage or exudate was present. The vessels showed moderate arteriovenous compression with slight beading. The arteriovenous ratio was essentially normal.

Laboratory studies revealed a normal blood count, sedimentation rate and urinalysis. The basal metabolism was −8. The electrocardiogram showed left axis deviation with no myocardial impairment. Nonprotein nitrogen was 31 mg. per cent. Creatinine was 1.1 mg. per cent. The Wassermann and Kahn tests were negative. Blood urea was 11.9 mg. per 100 cc. The urea clearance test was 89.4 per cent of average normal. The P.S.P. kidney function test was 52.3 per cent at the end of two hours. Fasting blood sugar was 81 mg. per cent.

Intravenous pyelograms were essentially normal. The first roentgenogram of the chest was taken on November 4, 1946, using the standards of Ungerleider and Clarke for all cardiac measurements; it was found that for a 26 year old patient, 60½ inches in height, weighing 132 pounds, the transverse cardiac diameter totaled 130 mm.; the predicted average normal is 126 mm., giving a 5 per cent enlargement (Table 1). The cold pressure test was positive. Heavy sedation had no effect upon the blood pressure. Spinal anesthesia did not lower the pressure. The patient was tried on barbiturates, xanthaline derivatives, rice and low sodium diets and potassium thiocyanate, but at no time was the systolic pressure lower than 220. Surgical intervention was repeatedly advised but was frowned upon by the family.

On September 8, 1947, while attending a football game, the patient was suddenly seized by a severe, acute knifelike epigastric pain which was severe enough to double her up and prevent her from assuming an erect position. Twelve hours later the pain radiated to the back and the patient became acutely ill. At this time, she was removed to St. John's Hospital, Santa Monica, California, for further observation. On arrival, it was found that the pain had spread to both lower quadrants. The temperature was normal. There were no chills, nausea or vomiting.

The patient lapsed into a semicomatose state and the physical examination revealed a blood pressure of 220 systolic, 120 diastolic in both arms. The second aortic sound was doubly accentuated over the pulmonic second sound. There was no difference in the pulsations in either arm. The blood pressure in both legs was 260 systolic, 160 diastolic. All deep reflexes were symmetrically diminished. Roentgenograms of the chest and flat plate of the abdomen, colon, kidneys and lumbar spine were essentially negative. The electrocardiogram revealed only left axis deviation.

The sedimentation rate on admission was 45 mm. per hour (Linzenmeier method). The blood count was normal. The urinalysis revealed a specific gravity

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of 1.014, 1+ albumin and an occasional red blood cell on microscopic examination. On the following day, September 9, 1947, the fasting blood sugar was 129 mg. per cent and the white blood count was 12,050 per cubic millimeter with 85 per cent neutrophils. The urinalysis revealed 2+ albumin; the carbon dioxide combining power was 67 volumes per cent.

By September 15, six days after admission, the patient was completely relieved of her pain and felt better. Further laboratory studies were done at this time, and it was found that the sedimentation rate had increased to 87 mm. per hour, the P.S.P. kidney function test was 52 per cent of normal at the end of two hours, and a two-hour kidney dilution test (Fishberg) produced 1.013 as the highest specific gravity. The systolic blood pressure remained between 220 and 240 mm. of mercury, and the diastolic pressure between 140 and 160 mm. A dissecting aneurysm was suspected, but could not be proved. On discharge, the patient was ambulatory and symptom-free.

The patient was well until October 26, 1947, at which time she developed a left hemiplegia with sluggish speech and drowsiness. She spoke out of the right side of her mouth, with weakness and loss of sensation in the left hand and left leg. Physical examination showed involvement of the left seventh cranial nerve, and a bilateral Babinski with positive left-sided Oppenheim and Gordon deep reflexes. It was felt that the diagnosis at this time was either a thrombosis or hemorrhage in the pons with lower motor neuron involvement. Two weeks later she became ambulatory with only residual left foot drop.

On November 20, 1947, the patient first complained of nocturnal dyspnea and exertional shortness of breath. Examination at this time revealed evidence of left ventricular failure, and the patient rapidly responded to digitalization and mercurial diuretics.

On January 2, 1948, the patient suddenly developed a swelling of the left side of the neck, left shoulder and left arm which extended from the mastoid process down to about 4 inches above the elbow. Distention of the venous circulation over the left shoulder was apparent. The blood pressure was 220 systolic, 140 diastolic. Radial pulsations were symmetrical.

For the first time, a faint, blowing, low-pitched diastolic murmur was present in the second interspace to the right of the sternum. Electrocardiographic tracings showed progressive left ventricular strain with a questionable healed anterior myocardial infarction pattern. Fluoroscopic studies showed hypertrophy and enlargement of the left ventricle; the ascending portion of the thoracic aorta was moderately prominent. The transverse and descending portions were widened considerably. The amplitude of the aortic pulsations was large in the ascending portion, but very small in the transverse and descending aorta.

The diagnosis at this time was essential hyperten-

ROBERT J. KOSITCHEK

TABLE 1

CHANGES IN SIZE OF HEART AND AORTA
(UNGERLEIDER AND CLARKE)

PLATE	DATE	TRANSVERSE CARDIAC DIAMETER	PREDICTED AVERAGE NORMAL	ENLARGEMENT, PER CENT	AORTIC SIZE	PREDICTED SIZE
			Preoperatively			
FIGURE 2	November 4, 1946	130 mm.	126 mm.	5	61 mm.	57 mm.
FIGURE 3	July 18, 1947	125 mm.	126 mm.	0	62 mm.	57 mm.
FIGURE 4	September 8, 1947	130 mm.	126 mm.	5	73 mm.	57 mm.
FIGURE 5	December 19, 1947	135 mm.	122 mm.	11	69 mm.	55 mm.
			Postoperatively			
FIGURE 6	April 30, 1948	122 mm.	122 mm.	0	72 mm.	55.3 mm.

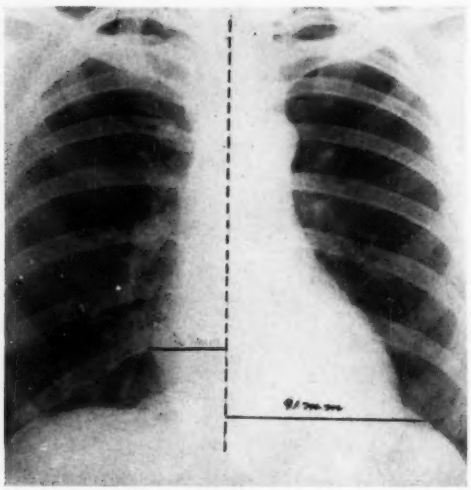

FIGURE 1. Roentgenogram taken November 4, 1946.

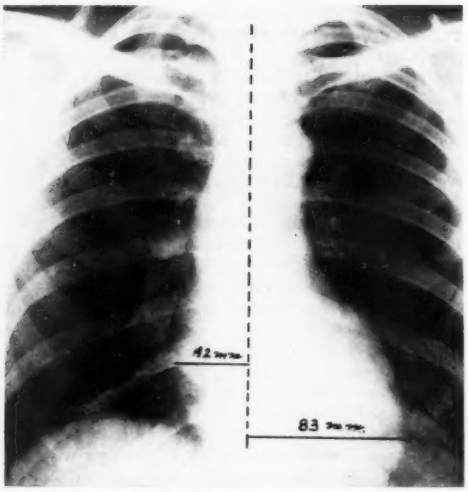

FIGURE 2. Roentgenogram taken July 18, 1947.

sion with cardiac enlargement, coronary artery insufficiency, cerebral thrombosis and a dissecting aneurysm involving the arch and descending portion of the aorta. It was felt that the aneurysm had infringed upon the venous circulation from the left side of the neck and the left arm. Figure 1 demonstrates the changes in size occurring within the heart and aorta.

The patient was referred to Doctor Howard Naffziger* on February 7, 1948. It was felt that she had a 25 per cent chance as an operative risk, and a 25 per cent chance for successful result from a sympathectomy. Without surgery, her prognosis for survival was less than six months.

The first stage Smithwick operation was performed on February 11, 1948, and the second stage was performed on March 5, 1948. The long delay between stages was necessitated by the stormy postoperative course following the first procedure. There was a substantial drop in blood pressure following the second operation.

The patient returned to her home on March 25, 1948, at which time the systolic blood pressure was 142 mm. of mercury. The patient gradually recovered her strength, and has been kept on a digitalization program and a low sodium diet. Two years later she appears to be in excellent health with a normal blood pressure, and a full home and social program. Her original complaints have all disappeared. The patient is symptom-free and apparently enjoying the best of health.

DISCUSSION

Most case reports on dissecting aneurysm have pathologic specimens to substantiate the diagnosis. However, in one respect we are fortunate that we have a living patient, and unfortunate that we cannot pathologically prove our diagnostic claims. All physicians interested in this patient feel that the history, physical findings, laboratory studies, roentgenograms, and clinical course fill all the criteria necessary for the antemortem diagnosis of dissecting aneurysm of the thoracic aorta.

A generation ago, when Herrick,[2] Levine and Trantner[3] first reported the fundamental observation in acute thrombosis of the coronary artery, the antemortem diagnosis of myocardial infarction was a medical condition which was readily recognized by most physicians. I believe that a somewhat analogous situation exists with the diagnosis of dissecting aneurysm of the aorta. The various clinical syndromes produced by this disturbance are gradually becoming clarified. There has been an increase in accurate diagnosis in the past decade, but Reich[4] has stated that "it only is through relentless correlation of postmortem findings with the clinical picture in individual cases that a true clinical consciousness of the disease can be adequately established."

Until we learn to recognize recovered cases of dissecting aneurysm, we will not be able to arrive at an approximation of the true incidence of dissecting aneurysm. Weiss[5] and co-workers believed that 1 out of 10 patients recover and die of other causes. Mote and Carr[6] in a five-year study from the coroner's office in San Francisco, found that 1.1 per cent of all cases of sudden death were due to dissecting aneurysm.

Interest in dissecting aneurysm of the aorta has been further stimulated by the findings of Baer

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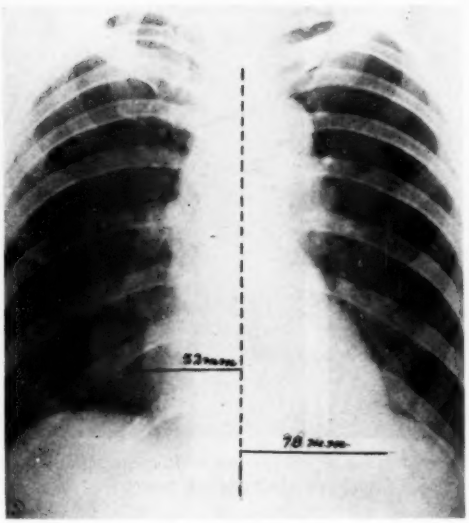

FIGURE 3. Roentgenogram taken September 8, 1947.

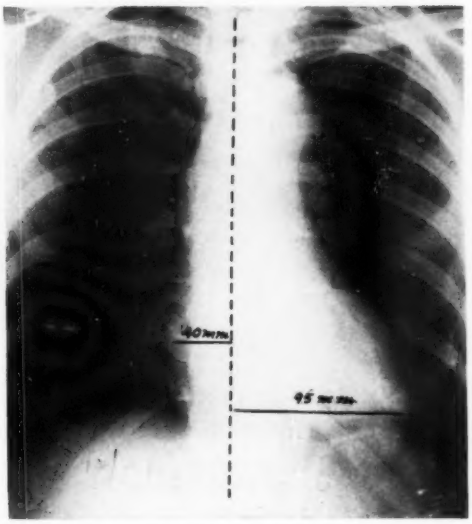

FIGURE 4. Roentgenogram taken December 19, 1947.

and Goldburgh[7] in their reporting of 44 cases. Their patients ranged in age from 35 to 82 years, the majority occurring in the fifth and sixth decades of life. Of the 44 cases reported by them, 62 per cent were men. Schnitker and Bayer,[8] in reviewing the literature up to 1943, were impressed with the occurrence of this condition in younger people. In the 580 cases they accepted as proved cases of dissecting aneurysm, gathered from the literature, 141 or 24 per cent occurred in individuals less than 40 years of age. Of those occurring in women, approximately 50 per cent were seen during pregnancy.

SYMPTOMS

The symptoms reported in the literature are variable. As a rule, the patient is suddenly seized with severe tearing or ripping pain in the chest or precordial area, or upper abdomen, collapse, sudden unconsciousness, or doubling in two. If consciousness is retained, the pain may increase greatly in intensity. The pain may radiate to the shoulder, back, renal area or groin, depending to some extent on the direction of the dissection and the various organs involved. The pain may be so intense that repeated injections of narcotics may fail to give relief. However, in many cases there may be no history of pain whatsoever. Cases have been reported in which pain has been absent during the entire course of the illness. In 24 of the 44 cases reported by Baer and Goldburgh,[7] there was no recorded history of pain at any time.

Dyspnea is also reported as an important symptom. Neurologic symptoms were present. Shock occurring with the tearing of the aorta would be so severe that syncope and collapse would develop. In some cases, the only history obtainable was the finding of the patient in coma. In other instances, agitation, disorientation, convulsive seizures, or bizarre peripheral neurologic signs may cause one to look to the cerebrum or spinal cord as the primary source of the trouble.

PHYSICAL FINDINGS

The physical findings vary greatly depending upon the length of time the patient survives, the age of the patient, pre-existing cardiovascular disturbance, and the vessels and organs involved in the dissection. If the patient survives the initial aortic tear, fever, tachycardia, and tachypnea usually develop. Hypertension is frequently present, but there is no question, however, that some cases, particularly those of younger individuals, fail to present evidence of hypertension in the history or physical examination or at necropsy. Cardiac enlargement, signs of cardiac failure, various cardiac murmurs, gallop rhythm or precordial rub may all be found. One important sign that may be almost pathognomonic of dissecting aneurysm is the development of the diastolic murmur of the aortic regurgitation. This murmur is apparently due to dilation or deformity of the aortic ring resulting from the dissection. The varied signs in the legs are due to the circulatory deficiencies resulting from the involvement of the intercostal, lumbar or femoral arteries.

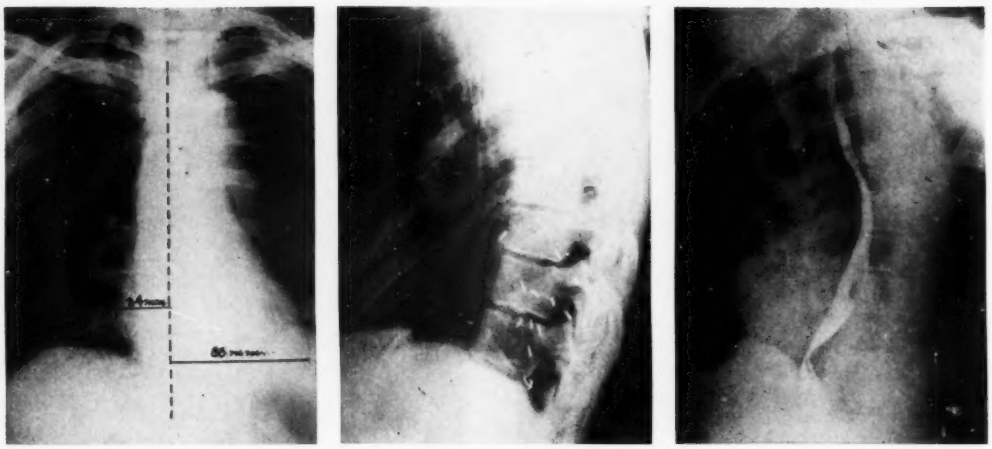

FIGURE 5. *(left)* Roentgenogram taken April 30, 1948. (Posteroanterior aspect.) *(center)* Roentgenogram taken April 30, 1948. (Lateral aspect.) *(right)* Roentgenogram taken April 30, 1948. (Left oblique aspect.)

LABORATORY FINDINGS

The laboratory findings are not overly significant. Leukocytosis has been a frequent finding and the urine may show a trace of albumin. Hematuria may be present if the dissection has approached or involved the renal arteries. Electrocardiographic changes are most significant. Roentgenologic examination may also be of some help in the differential diagnosis. There is a deformity of the aortic or supercardiac shadow. This may gradually or rapidly increase in size.

PATHOLOGY

Pathologically speaking, the process involved in dissection of the aorta may be described as follows: The primary change in the aorta is a cystic degeneration of the media, the so-called Erdheim's medionecrosis cystica. The cause of this degeneration is not certain. In this type of aorta there occurs a rupture in one or more medial nutrient vessels into one of the cystic spaces producing a hematoma. The hematoma enlarges, splitting the layers of the media and the intima is then secondarily torn. An opening is thus made into which the large aortic column of blood may force itself and produce varying degrees of dissection along the medial coat. The dissection which begins in the ascending aorta in over 70 per cent of the cases may also extend cuspward. Some writers feel that the dissection backward toward the cusps is responsible for distortion of the aortic ring and the resultant diastolic murmur which is such a valuable diagnostic sign. Hypoplasia and coarctation of the aorta may be additional pathologic findings for the cause of the dissection.

REFERENCES

1. Willius, F. A., and Cragg, R. W.: Cardiac clinics: Talk on dissecting aneurysm of the aorta. Proc. Staff Meet., Mayo Clin. 16:41, 1941.
2. Herrick, James B.: Thromboses of coronary arteries. Tr. A. Am. Physicians 33:408, 1918.
3. Levine, S. A., and Trantner, C. L.: Infarction of the heart. Am. J. M. Sc. 155:57, 1918.
4. Reich, N. E.: Dissecting aneurysm of the aorta. Clinics 3:346, 1941.
5. Weiss, Soma, Kinney, T. D., and Maher, M. A.: Dissecting aneurysm of the aorta. Am. J. M. Sc. 200:192, 1940.
6. Mote, C. D., and Carr, J. L.: Dissecting aneurysm of the aorta. Am. Heart J. 24:65, 1942.
7. Baer, S., and Goldburgh, H. L.: The varied clinical syndromes produced by dissecting aneurysm. Am. Heart J. 35:198, 1948.
8. Schnitker, M. A. and Bayer, C. A.: Dissecting aneurysm of aorta in young individuals, particularly in association with pregnancy, with report of case. Ann. Int. Med. 20:486-511 (March) 1944.

CLINICAL STUDY

Topical Anesthesia in Dermatology

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For a long time we have sought a topical analgesic that would offer sustained relief from surface pain and itching but would obviate the disadvantages of older agents.

The authors have had a high degree of success in relieving painful and pruritic dermatoses with a topical anesthetic ointment incorporating 20 per cent dissolved benzocaine with oxyquinoline benzoate in a bland, water-soluble base.† The ointment is neither sticky nor tacky, is easy to apply and can be removed with plain water. It is colorless, nonstaining and practically odorless, and can be covered with a bandage or other protection. Antipruritic action is prompt on both intact and broken skin, and relief lasts from three to six hours.

Tainter pointed out that benzocaine is the best topical anesthetic when a concentration of at least 10 per cent can be secured.[1] Heretofore solutions of approximately 2 per cent benzocaine have been considered the maximum; however, higher concentrations in alcohol, chloroform and ether have been obtained, but are of little value for topical use in dermatology because of relatively high incidence of irritation and rapid evaporation of the vehicle, resulting in deposits of benzocaine crystals rather than dissolved benzocaine.

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†Furnished by Americaine, Inc., Evanston, Illinois.

Our interest in benzocaine was further prompted by the fact that it is the least toxic of the drugs generally used in topical anesthesia. Adriani, for example, made a study of the relative toxicity of such anesthetics. Using cocaine for the standard, the results were as follows:[2]

Benzocaine	1/10	LAROCAINE®	1
Procaine	¼	HOLOCAINE®	2
METYCAINE®	¾	BUTYN®	2½
DIOTHANE®	¾	PONTOCAINE®	3 to 5
Cocaine	1	NUPERCAINE®	5

CLINICAL STUDY

The 20 per cent dissolved benzocaine ointment was used in the treatment of 132 cases, including 22 types of dermatologic conditions. Patients were instructed to apply the ointment liberally to the affected area and to renew applications as required. Relief from pruritus was obtained in every condition treated except lichen simplex chronicus (see Table 1).

COMMENTS

There was no evidence of irritation or sensitization caused by the benzocaine, although 2 cases of dermatitis venenata exhibited exacerbations. Relief was noticed faster on broken skin than on intact skin. Relief on mucous surfaces was rapid but not as sustained as that on the skin.

Infantile eczema—The ointment was used on both dry and weeping conditions. In weeping conditions, the ointment was mixed equal parts with

TABLE 1

RESULTS OF TOPICAL ANESTHESIA WITH 20 PER CENT DISSOLVED BENZOCAINE OINTMENT IN 132 CASES

CONDITION	NUMBER OF CASES	DURATION OF RELIEF OF PRURITUS (HOURS)
Atopic dermatitis, infantile eczema	10	3-5
Atopic dermatitis, adult	6	4 cases 3-4 2 cases unsatisfactory
Lichen simplex chronicus	2	Unsatisfactory
Eczematoid neurodermatitis	4	3-5
Menopausal neurodermatitis	2	3-5
Urticaria, localized	5	3-5
Infectious bacterial eczematoid dermatitis	5	3-5
Eczematoid stasis dermatitis	4	3-4
Dermatitis venenata	4	2 cases 3-5 2 exacerbations
Intertrigo	4	3-5
Postscabetic pruritus	15	3-5
Pruritus vulvae, nonspecific	5	4-5
Pruritus ani	5	1-3
Pruritus, scalp, nonspecific	3	2-5
Lichen planus	6	2-5
Pityriasis rosea	5	2-4
Pruritus senilis	5	3-4
Traumatic ulcer	3	4-5
Varicose ulcer	10	4-5
Chronic otitis externa eczematization	8	3-5
Furuncle, ear (relieve pain)	6	Satisfactory
Actinic burns	15	3-5

CLEVELAND J. WHITE

Lassar's zinc oxide paste to aid absorption of serous discharge. Relief was both rapid and sustained.

Varicose ulcers—In these cases, the ointment with 0.08 per cent incorporated chlorophyll was used, together with supportive therapy. The pain was relieved and, after circulatory repair measures, healing occurred.

Lichen simplex chronicus—Ointment did not give relief in these 2 cases. The benzocaine apparently could not penetrate the thick keratinized layer.

Sunburn—The ointment alone provided prompt relief. By adding an equal amount of petrolatum, the anesthetic quality of the ointment was obtained, plus the lubricating effect of the petrolatum.

Otitis externa eczema—A topical anesthetic may be helpful by allowing the tissue to rest. The ointment provided prompt and sustained relief in some cases.

SUMMARY

THE authors used an ointment containing 20 per cent dissolved benzocaine in 132 cases of various dermatoses and obtained prompt, sustained relief in 128 cases. There were no cases of irritation or sensitivity which could be directly attributed to the ointment or the incorporated benzocaine, although 2 cases of dermatitis venenata (poison ivy) exhibited exacerbations. Dissolved benzocaine is apparently a highly safe and effective means of topical anesthesia for use in many dermatologic conditions.

REFERENCES

1. TAINTER, M. and WINTER, L.: Some general considerations in evaluating local anesthetic solutions in patients. Anesthesiology 5:470 (September) 1944.

2. ADRIANI, J.: The Pharmacology of Anesthetic Drugs. Springfield, Illinois, Charles C Thomas, 1941, p. 49.

GENERAL PRACTICE *Review*

To provide the general practitioner, as well as the specialist, with concise, readily available information on the latest, proved methods of treatment of conditions commonly encountered in an average practice, POSTGRADUATE MEDICINE *offers this department to its readers. It is not, of course, intended to present these discussions as the only acceptable therapeutic procedures to be used, but rather to offer simple regimens and recommendations based on the extensive experience of the physicians who prepared these summaries.*

The Present Status of Acute Respiratory Infections

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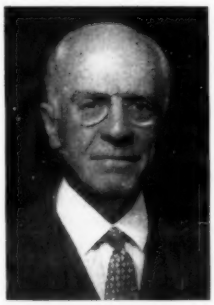
NEW YORK CITY



CECIL

ACUTE respiratory infections are caused by viruses, bacteria, and occasionally by rickettsiae. In the present discussion I propose to limit myself largely to the viral infections. I will also touch briefly on the more common bacterial infections, such as those of pneumococcal or streptococcal origin. The only respiratory rickettsial infection of any moment is the so-called Q fever, several epidemics of which occurred in American troops during World War II. Q fever may manifest itself as an acute upper respiratory infection which often takes on the form of an atypical pneumonia.[1] It is caused by an obligate intracellular parasite, the *Rickettsia burneti*. The diagnosis can be made by demonstration of agglutinins against *R. burneti* in the serum of the patient.

The great majority of acute upper respiratory infections are caused by some type of virus. Viruses can of course cause pneumonia also, but the majority of pneumonias in man are due to some pathogenic micrococcus or bacillus.

The nature of viruses is not yet clearly understood, but certain facts are fairly well established. They are tiny entities which can be seen by a sufficiently powerful microscope, and we also know that multiplication of viruses occurs under suitable conditions in the presence of living cells. In the absence of living cells no virus has as yet shown any capacity for multiplication. Viruses differ greatly in size, stability and degree of structural differentiation. The smaller viruses, such as those responsible for foot-and-mouth disease and poliomyelitis, are particles no larger than serum globulin molecules. The larger viruses, such as those of psittacosis and vaccinia, are almost equal in size to that of certain bacteria. There has been much discussion on the question of whether viruses are living or non-living entities. They possess some qualities which are essentially characteristic of living things, and certain others which we usually associate with non-living matter. It is not yet known just how they should be classified. The present tendency, however, is to look upon viruses as extremely small intracellular parasites.

It is a recognized fact that viruses affect the same cells in different ways, and it is well established that certain viruses selectively attack different types of cells. This explains why virus diseases present such extremely diverse clinical pictures; even the pathological changes are quite dissimilar.

Let us now consider some of these acute respiratory infections which are caused by viruses.

THE COMMON COLD

It has been shown by numerous observers that the nasal secretions of many persons suffering from acute coryza harbor a virus which when instilled into the nostrils of normal individuals reproduces the disease. Dochez and his co-workers[2] succeeded in cultivating this agent in embryonic tissue media and have indicated that it should be classified among the filterable viruses. Most colds, particularly those occurring in epidemic form, are probably caused by a virus or a group of viruses. On the other hand, it would be a mistake to consider all common colds as virus-borne; particularly in young children and babies a good many acute respiratory infections are caused by pathogenic cocci, such as the pneumococcus and hemolytic streptococcus.

We know very little at present about immunity to the cold virus. We do know there are many people who practically never have a cold, while others are highly susceptible and will suffer from five or six colds a year. From my own personal observation I would say that tense, nervous, undernourished individuals are more likely to be susceptible, while the opposite type has a comparatively good immunity. Most allergic individuals are susceptible to colds, and certainly a chronic sinus infection predisposes to frequent flare-ups.

Subsequent to the initial injury to the epithelium caused by the cold virus, bacteria already present in the respiratory tract assume the role of secondary invaders and may give rise to further symptomatology.

I think every physician will agree that complications make the cold problem. The four or five day course of a common cold such as one sees in healthy young adults is not a problem to worry about. However, when the secondary invaders arrive, and when the sinuses become acutely infected or the ears involved, or possibly a pneumonia develops, then the problem becomes a serious one. Personally I have long suspected that in the case of these complications the virus actually starts the trouble. In other words, the virus itself invades the sinuses, trachea, or the eustachian tube, and the bacteria follow.

INFLUENZA

Influenza is also a specific infectious disease caused by a filterable virus, but it is a much more highly contagious disease than coryza and tends to occur in epidemic and pandemic outbreaks during which it spreads with extraordinary rapidity. Comparatively mild epidemics of influenza occur almost every winter in some parts of the United States; the pandemics, however, are much less frequent and much more severe. During a pandemic the morbidity rate is very high, the best statistics placing it at approximately one out of every three individuals. Though people of all ages are susceptible, the highest incidence is among young adults. Other features of influenza are the explosive nature of the outbreak, the rapidity of its spread, and the relatively short duration of the epidemic. During the severe visitation in 1918 most of the epidemic was over in a comparatively few weeks.

Shortly after the great influenza epidemic of 1918, Dr. Francis Blake and I were stationed at the U. S. Army Medical School in Washington where we were working on experimental pneumonia in monkeys. Because of our success in producing experimental *Hemophilus influenzae* infections in monkeys (not only tracheitis and sinusitis, but pneumonia as well) we were led to believe that this organism, then called the Pfeiffer bacillus, was responsible for the epidemic.[3] However, this point of view was later proved to be incorrect.

It was not until 1933, 15 years after the great epidemic, that Smith, Andrews and Laidlaw[4] demonstrated that influenza was caused by a filterable virus. They achieved this important discovery by inoculating ferrets intranasally with filtrates of throat washings obtained from patients with influenza early in the course of the disease. The virus was transmitted from ferret to ferret and subsequently to mice. It is readily propagated in the chorio-allantoic fluid of embryonated hens' eggs. These observations by Smith and his co-workers have been amply confirmed by other investigators.

At least two distinct strains of influenza virus have been identified; these are known as A and B, respectively. Either of these strains is capable of inducing an influenza-like infection in man, when the active virus is introduced into the respiratory tract of the subject.[5,6] It seems quite likely that still other strains will be isolated as time goes on. It is important to remember that these viruses A and B were both recovered from local epidemics and not from the pandemic of 1918.

Whether pandemic influenza will be found to be due to a strain of virus different from those so far identified, or will prove to be a symbiotic infection comparable to swine influenza, only future study can determine. Shope[7] has proved conclusively that swine influenza is caused by a combination of virus and a gram-negative bacillus very similar in its morphology to the Pfeiffer bacillus. It is therefore quite possible that the pandemic form of influenza in man is caused by a virus in symbiotic combination with the *H. influenzae* of Pfeiffer. The most frequent secondary invader during the pandemic was the *H. influenzae* and at autopsies it was frequently encountered in the pus from infected sinuses and in the exudate throughout the bronchi and bronchioles. It was less frequently found in the parenchyma of the lung and only rarely invaded the pleura. The other important secondary invaders were of course the pneumococcus, streptococcus and *Staphylococcus aureus*.

At the time of the great pandemic of 1918 the writer was stationed at Camp Wheeler, Georgia. The epidemic struck in October when the weather was still quite warm. It spread with lightning rapidity among the troops, many of whom were colored. As I recall this rather terrifying experience, certain features stand out vividly. It was not so much the upper respiratory symptoms, such as cough, sore throat and coryza, as it was the high fever, intense muscular aching and extreme prostration which were conspicuous. Many of these patients also had a marked leukopenia. Another interesting feature was the tendency, in a good many cases, for the virus to go straight to the lung, producing the so-called pneumonic form of influenza with few if any preliminary symptoms in the upper respiratory tract.

The pneumonia which we saw was of two types: (1) ordinary lobar or lobular pneumonia, caused by the pneumococcus or streptococcus, and (2) a diffuse purulent bronchiolitis and peribronchiolitis, quite similar in pathology to present-day virus pneumonia, except for the intense hemorrhage and edema which accompanied it. The bronchiolitic type of influenzal pneumonia was often associated with almost pure cultures of the *H. influenzae*. The fatality rate for this pandemic form of influenzal pneumonia was amazingly high, considering the fact that most of the victims were healthy young adults. It varied in different training camps from 30 per cent to 60 per cent. This was of course long before the days of antibiotic therapy.

A. R. D.

A discussion of acute respiratory epidemics among soldiers naturally leads to consideration of the interesting epidemics which have been described by the Commission on Acute Respiratory Diseases at Fort Bragg, N. C.[8] This committee, headed by Dr. John H. Dingle, observed repeated epidemics of acute respiratory disease among new recruits, occurring most commonly during the winter months, and characterized by fever and acute upper respiratory symptoms. The agglutination tests on these recruits definitely ruled out either A or B types of influenza. Whether similar epidemics occur in civilian life the authors are unwilling to say. These studies were based solely on hospitalized cases of respiratory disease. The authors found it impossible to determine whether or not these infections which they observed among new recruits at Fort Bragg correspond with the common forms of acute respiratory disease, such as the common cold, which so frequently are seen in civilian life. They deemed it reasonable to suppose that they did, but the total lack of adequate means of differential diagnosis prevented elucidation of this point.

In later articles the Commission showed that these minor respiratory illnesses in recruits could be transmitted to human volunteers by the use of bacteria-free filtrates of nasal and pharyngeal washings obtained from infected donors.[9] Two independent filterable agents, presumably viruses, were isolated, thus indicating that there was more than one virus capable of producing minor respiratory illness in man. Two distinct types of experimentally produced minor respiratory illness resulted, (1) a coryza-like infection with a short incubation period of one to two days, and (2) an infection developing after five or six days, and characterized by prominence of sore throat and minimal nasal symptoms.

VIRAL PNEUMONIA

As far back as the pandemic of influenza in 1918 Goodpasture described instances of bacteria-free pneumonia. These cases were probably caused by the influenza virus which at that time had not been isolated. Further evidence of viral pneumonia began to appear with reports in the literature of atypical pneumonic infiltrations produced by such virus-borne diseases as measles, vaccinia, variola, and lymphocytic choriomeningitis. It is interesting that in influenzal pneumonia of either A or B type the virus of this disease rarely appears in the lungs in pure culture. It is nearly always associated with pathogenic cocci or Pfeiffer's bacillus. Strangely enough, however, when the virus of influenza is inoculated into mice, the animals almost invariably develop pure virus pneumonia, usually without involvement of the nasal or pharyngeal epithelium. Finally there are the comparatively rare viral pneumonias such as those caused by the psittacosis group of viruses, some of which have an extremely high death rate.

Following the classification of Reimann[10] we can now discuss briefly those pneumonias which are *probably* of viral origin. Among such we would include the pneumonia of infectious mononucleosis, the pneumonia of erythema multiforme and some of the unclassified viral pneumonias of infants. Undoubtedly the most important of the viral pneumonias in this group is the so-called "primary atypical pneumonia of unknown cause." This type of pneumonia has probably existed for an indefinite period of time, but only in recent years has it come into prominence because of its great prevalence. This high incidence of atypical pneumonia was particularly noticeable during the late thirties and early forties. Indeed for a time, it became so common that it looked as though it might replace ordinary lobar pneumonia completely.

Atypical pneumonia may occur in sporadic form, but more frequently it occurs in epidemics, at which time it is accompanied by an increase in the incidence of common colds, grippe, pharyngitis and other mild respiratory infections, presumably

all of the same etiology. Because of its low death rate, comparatively few cases of atypical pneumonia have come to autopsy. However, fatal cases which have been studied show that the disease cannot be distinguished pathologically from that caused by other viruses. The histologic picture is that of interstitial pneumonitis with bronchiolitis, quite similar to that observed in influenzal pneumonia. However, there is not the same tendency to edema and hemorrhage that is characteristic of influenzal pneumonia.

The incubation period is usually a week to 10 days, in some cases even longer. As a rule the onset is not abrupt, the disease coming on gradually and often without any preceding upper respiratory symptoms such as pharyngitis or coryza. There is of course a mild form of this infection in which the lungs show little or no involvement, even by x-ray. These patients present the usual picture of an acute upper respiratory infection with headache, malaise, anorexia, weakness and unproductive cough. In the mild attacks there is slight if any fever or rhinorrhea.

However, the disease in its typical form is a pneumonia, though the pneumonia usually runs a mild course. The symptoms are remittent fever which is seldom very high, relatively slow pulse, normal or slightly increased respiration rate, physical signs which are quite at variance with the roentgenographic evidence of pulmonary invasion, cough which is often nonproductive but markedly paroxysmal, a normal or slightly elevated leukocyte count, and recovery by lysis with few complications. In the latter respect it differs widely from classic influenzal pneumonia such as occurred in 1918, where a very high percentage of cases were complicated by empyema or pericarditis.

Agglutination of the patients' red blood cells, the so-called cold agglutination reaction, occurs in about 55 per cent of viral pneumonias. There is considerable difference in its incidence in different epidemics. For example, in certain outbreaks a positive cold agglutination reaction was reported in over 90 per cent of patients. The reaction usually becomes positive in the second week of the pneumonia and often persists after recovery. Unfortunately the cold agglutination reaction occurs in many other diseases, though not in such a high titer as in virus pneumonia. Because of its late appearance the test is not of great value as a diagnostic measure.

All observers are agreed as to the usual disproportion between the x-ray evidence of pulmonary involvement and the sparse physical signs. The consolidation is usually greatest near the hilum, but the shadow is rarely as dense as that of pneumococcal pneumonia. Sometimes scattered areas of pneumonia may coalesce to form fairly large patches.

The complications of viral pneumonia are few compared with influenzal or ordinary lobar pneumonia. Pleural effusions occasionally occur. Encephalitis and meningomyelitis have been noted in a few cases.

In 1946 the Commission on Acute Respiratory Diseases at Fort Bragg, N. C., reported successful transmission of primary atypical pneumonia to human volunteers.[11] Conscientious objectors were used for the tests. Respiratory illness having all the characteristics of primary atypical pneumonia was observed in the individuals whose respiratory tract was sprayed with sputum and throat washings of patients with virus pneumonia. Infection was carried thus through two successive groups of well persons. The further successful transmission of the disease with bacteria-free filtrates would indicate that atypical pneumonia is caused by a virus. The clinical features of experimentally induced atypical pneumonia were quite similar to those of the naturally acquired disease. This was true also of the physical signs and the x-ray picture. The experimental disease also showed a high cold agglutination reaction. Thus it would seem that what we have always suspected was about to be proved true—namely, that so-called "primary atypical pneumonia of unknown etiology" is really just one more type of virus pneumonia.

LOBAR PNEUMONIA

Lobar pneumonia, after having been crowded out of the picture for several years by atypical virus pneumonia, appears to be coming back into its own again. Certainly that is true of the New York district, with which I am most familiar. However a considerable number of atypical virus pneumonias still turn up from time to time.

TREATMENT OF ACUTE RESPIRATORY INFECTIONS

The treatment of the common cold, as we all know from painful experience, is almost entirely symptomatic. The aspirin, acetophenetidin and caffein mixtures are rightly popular, and to this may be added codeine, depending on the severity of the symptoms. There has been much advertising of the various vasoconstrictors which are used locally in the form of an atomizer. These give temporary relief, but may be followed by secondary hyperemia, edema and irritation of the mucous membrane when used to excess. I saw a patient not long ago whose nose became so completely blocked up from edema following the use of one of these vasoconstrictors that he was unable to breathe through the nose for two or three weeks. Patients should be advised to employ these vasoconstrictor drugs only during the acute phase of the cold and not more frequently than once every four hours.

Various "antihistamine" agents have been advocated for the treatment of coryza, and a number of recent statistical studies have lent support to the theory that antihistaminics, by controlling the allergic features of the cold, would bring about its prompt resolution. While it is true that antihistaminics will often give temporary relief to the early swelling and rhinorrhea, these agents are in no sense a cold cure. Furthermore, the dizziness and drowsiness which they often induce may prove to be more objectionable than the cold itself. The writer believes that for these reasons, antihistaminics are destined to only a brief popularity.

Neither the sulfonamides nor the antibiotics have any specific effect on the virus which causes the common cold. There is therefore no indication for the routine administration of these agents in the treatment of an ordinary uncomplicated coryza. It should be added, of course, that the antibiotics have a real function in the treatment of secondary bacterial infections, such as acute sinusitis or otitis media. In such cases penicillin or the newer agents, such as aureomycin, chloramphenicol and terramycin, can be used with benefit, but these products are much more effective when given internally than when applied locally on the surface of the mucous membrane. The dose of penicillin is 300,000 units a day intramuscularly; of the others 250 to 500 mg. by mouth four times a day. These newer antibiotics, when taken by mouth, may cause considerable gastrointestinal disturbance in some patients.

While in the majority of cases the common cold is a trivial infection, there is a goodly number for whom coryza is a much more serious problem. These patients know from past experience that complications in the sinuses, ears or trachea are going to follow. In a good many children the middle ear has a rather terrifying way of lighting up with every coryza. It is in this group of patients that antibiotic therapy has its important field. However, even here I don't believe that antibiotic treatment will be generally successful unless the complication at the same time receives adequate local treatment and, if necessary, surgical drainage. With drainage antibiotics should be effective.

The treatment of influenza differs in no essential respect from that of the common cold. The most important features of the treatment are (1) absolute confinement to bed from the onset of the disease until convalescence is well established; (2) administration of large quantities of fluid, and (3) isolation of the patient from sources of secondary infection, and the practice of medical asepsis by those coming in contact with the patient. During the great pandemic of 1918 we discovered after it was too late that influenza patients who were left in barracks had a much lower incidence of complications, particularly pneumonia, than those who were transferred to a ward in a base hospital, where they were immediately exposed to pathogenic bacteria from patients in adjacent beds. For the marked prostration, usually accompanied by cold clammy skin, small frequent doses of alcohol are helpful. For the very sick patients penicillin should be used by mouth or intramuscularly as a prophylactic.

The treatment of influenzal pneumonia does not differ from that of any other type of pneumonia; both symptomatic and specific therapy are usually indicated.

Treatment of virus pneumonia. The symptoms of virus pneumonia are treated as they appear, just as one would treat any case of pneumonia. Both penicillin and sulfonamides have proved to be without value. The new antibiotics, aureomycin, chloromycetin and terramycin apparently control rickettsial infections and are also proving to be of value in virus pneumonias. It should be added that in many cases of atypical pneumonia the physician cannot be sure whether he is dealing with a true virus pneumonia, or with an atypical pneumococcal or streptococcal infection. In such a situation, particularly if the patient is acutely ill, it is far better to administer penicillin for 48 hours on the chance that one may be dealing with a bacterial infection. If no benefit results after 48 or 72 hours, penicillin should be discontinued and treatment with one of the newer antibiotics substituted.

There is nothing much that I can add to the already well standardized treatment of *pneumococcal* and *streptococcal pneumonia* with antibiotics. Penicillin has proved to be such a dramatic agent that sulfonamide drugs have been pushed somewhat into the background. We must never forget, however, that sulfadiazine is still an excellent agent for the treatment of pneumococcal and streptococcal pneumonia. It has been found that lobar pneumonia can be controlled by oral administrations of penicillin in doses five times as large as would be used intramuscularly. However, for severe infections we still recommend the intramuscular route, 300,000 units of crystalline procaine penicillin once or twice every 24 hours, and this should be continued for two or three days after the crisis.

For the rare but very serious *Friedländer's bacillus infections* it is necessary to resort to streptomycin combined with penicillin. The dosage of streptomycin in these cases should be 2 gm. a day intramuscularly in 0.5 gm. doses four times a day, with 300,000 units of procaine penicillin twice a day intramuscularly until the infection is well under control. *H. influenzae pneumonia* is very rare in adult life. Antibiotic therapy is the same as for Friedländer infections. Always give penicillin with streptomycin to combat possible drug resistant variants.

SUMMARY

In summary, we may conclude that while much knowledge has been gained during the past two

decades concerning the nature and diagnosis of acute respiratory infections, there is still much to be learned, especially regarding the virus-borne group. With respect to treatment, the antibiotics have proved to be of great value in controlling pathogenic micrococci, and of definite aid in the fight against viruses. The introduction of certain new antibiotics such as aureomycin, chloramphenicol and terramycin mark the first steps toward a more efficacious control of viral infections of the respiratory tract.

REFERENCES

1. Feinstein, M., Yesner, R. and Marks, J. L.: Epidemics of Q fever among troops returning from Italy in the spring of 1945. I. Clinical aspects of the epidemic at Camp Patrick Henry, Virginia. Am. J. Hyg. 44:72 (July) 1946.
2. Dochez, A. R., Mills, K. C. and Kneeland, Yale, Jr.: Study of the virus of the common cold and its cultivation in tissue medium. Proc. Soc. Exper. Biol. & Med. 28:513, 1931.
3. Blake, F. C. and Cecil, R. L.: Studies on experimental pneumonia. II. Pathology and pathogenesis of pneumococcus lobar pneumonia in monkeys. J. Exper. Med. 31:445, 1920.
4. Smith, W., Andrews, C. H. and Laidlaw, P. P.: A virus obtained from influenza patients. Lancet 2:66, 1933.
5. Francis, T., Jr., Salk, J. E., Pearson, H. E. and Brown, P. N.: Protective effect of vaccination against induced influenza A. J. Clin. Investigation 24:536 (July) 1945.
6. Salk, J. E., Pearson, H. E., Brown, P. N. and Francis, T., Jr.: Protective effect of vaccination against induced influenza B. J. Clin. Investigation 24:547 (July) 1945.
7. Shope, R. E.: Swine influenza; filtration experiments and etiology. J. Exper. Med. 54:373, 1931.
8. Commission on Acute Respiratory Diseases: Acute respiratory disease among new recruits. Am. J. Pub. Health 36:439 (May) 1946.
9. Commission on Acute Respiratory Diseases: Experimental transmission of minor respiratory illness to human volunteers by filter-passing agents. II. Immunity on reinoculation with agents from the two types of minor respiratory illness and from primary atypical pneumonia. J. Clin. Investigation 26:974 (September) 1947.
10. Reimann, H. A.: The viral pneumonias and pneumonias of probable viral origin. Medicine 26:167 (May) 1947.
11. Commission on Acute Respiratory Diseases: The transmission of primary atypical pneumonia to human volunteers. Bull. Johns Hopkins Hosp. 79:97 (August) 1946.
12. Rivers, T. M.: Recent advances in the treatment of viral and rickettsial diseases. J.A.M.A. 136:291 (January 31) 1948.
13. Cecil, R. L.: Chemotherapy in acute upper respiratory infections. Bull. New York Acad. Med. 21:263 (May) 1945.
14. Bunn, P. A., McDermott, W., Hadley, S. J. and Carter, A. C.: Treatment of pneumonia with oral penicillin. J.A.M.A. 129:320, 1945.
15. Francis, T., Jr. and Salk, J. E.: A simplified procedure for the concentration and purification of influenza virus. Science 96:499, 1942.
16. Van Ravenswaay, A. C.: Prophylactic use of influenza virus vaccine. J.A.M.A. 136:435 (February 14) 1948.
17. Francis, T., Jr., Salk, J. E. and Quilligan, J. J.: Experience with vaccination against influenza in spring of 1947. Am. J. Pub. Health 37:1013 (August) 1947.
18. Sigel, M. M., Shaffer, F. W., Kirber, M. W., Light, A. B. and Henle, W.: Influenza A in a vaccinated population. J.A.M.A. 136:437 (February 14) 1948.
19. Cecil, R. L., and Austin, J. H.: Results of prophylactic inoculation against pneumococcus in 12,519 men. J. Exper. Med. 28:19, 1918.
20. McLeod, C., Hodges, R. G., Heidelberger, M. and Bernhard, W. J.: Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. J. Exper. Med. 82:445, 1945.
21. Robertson, O. H.: Sterilization of air with glycol vapors. Harvey Lectures, Series 38, 227, 1942-43.
22. Bloomfield, A. L.: Some of the problems of the common cold. J.A.M.A. 144:287 (September 23) 1950.

Treatment of Acne

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Acne still is one of the common diseases of the skin observed in general practice, and the majority of the cases are seen first by the general practitioner. It is the general practitioner also, with his care of the family group, who has the enviable opportunity to observe the early developments of acne in children. It is the rare child who escapes from some manifestations of acne as this child reaches puberty.

GOLDMAN

Because of the importance of acne to the child and the continued emphasis on this condition in the advertising media of the day, the practitioner must realize the significance of the disorder and be sympathetic with the patient even though the skin manifestations may seem so trivial in comparison with the overwhelming majority of more serious disorders observed by him. Moreover, the early treatment of acne can do much to prevent the development of the more severe forms with their intractable and disfiguring scarring.

It seems best to consider the treatment of acne in relationship to various age groups. It is our feeling from studies of families with the severe forms of acne that the children of these families may show early manifestations of the condition long before the expected time of puberty. Therefore, if the practitioner has under his care a family

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group with manifestations of the severe nodulocystic scarring forms of acne, it is his duty to watch the younger members of this family as they grow up so that treatment may be started in the early phases, irrespective of their age. If the young child, before puberty, starts to develop a significant number of comedones about the forehead, nose and chin, along with early development of pustules, and especially nodules, then a local treatment regimen should be instituted.

LOCAL TREATMENT

In brief the principles of local treatment are the attempts to dry the skin through external measures and to relieve any secondary infections which may occur. At least for the young child, any investigative procedures to attempt to control the secretion of sebum should not be used at present.

The treatment program in the young child includes vigorous and repeated washings of the face with a wash cloth; it is not necessary to subject the child to the use of a strong brush or to expose him to steaming of the face. The washing may be done with any type of detergent. In our present state of knowledge, it is not possible to state positively that certain types of detergents are more effective than others. In our Acne Research Project, we are studying the use of different types of detergents; at present we can state only that for the excessively greasy skin, detergents which are ordinarily considered as strong seem able to dry the skin more quickly than the milder type of toilet soaps. Such measures as tincture of green soap, abrasive soaps, etc., may be used for the child with the very greasy skin. Detergents with hexachlorophene are under study now also. The washing should be done at least three times a day and they should be done by the parent if the child will not cooperate.

As a further attempt to dry the skin, 70 per cent alcohol may be rubbed on the skin with a piece of cotton twice a day. Exposure to sunlight should be encouraged as much as possible since this also aids in drying the skin. However, exposure to heat or humidity will aggravate the condition. If the child is not aware of his condition or is not self-conscious about it, then only this simple local treatment routine should be pursued in a matter-of-fact fashion. The overanxious parent should attempt to emphasize it as little as possible.

If the child has already become self-conscious about the condition, then he must be instructed that no picking, squeezing or excoriating of the lesions is allowed, since these measures may aggravate. In addition, for the self-conscious child, attempts should be made to cover up the condition as much as is cosmetically possible. This will be discussed later on. One should make an effort to understand and to sympathize with the "excoriating personality" pattern. If the comedone phase is excessive, large doses of vitamin A may be used in an attempt to correct this. The dosage and the duration of vitamin A therapy depend to some degree on the response of the child. The new types of water-dispersible vitamin A mixtures lend themselves readily for this purpose.

FURTHER THERAPY

If the phase of secondary infection becomes more marked and pustules and even nodules develop, then local therapy has to become more vigorous. In addition to the cleansing and drying routines described, the use of medicated topical applications and additional systemic therapy becomes necessary.

If both the child and the mother are of the anxious type, then it is better not to do frequent incisions, drainages, comedone extractions, etc. It is well to have the parent understand from the beginning that scarring results from the destruction of tissue, not simply from the incision and drainage of lesions of acne. In a study of the psychosomatic aspects of acne to appear in the future, the role of the parent in the background of acne will be detailed. However, if a lesion becomes progressively deeper and actually burrowing, then drainage must be secured in order to lessen the amount of scarring.

The comedone extractor instrument per se must not be used to open up pustules; such lesions are picked open with a small type of splinter forceps or nicked gently with a cataract knife. These technics refer to the relatively superficial type of pustules and small nodules. The deep nodulocystic lesions will be considered later, since this form rarely occurs in the young child. Any lesion which does not show a visible degree of superficial pustulation on the skin or which is deep or throbbing, should not be subjected to incision, but should have hot wet packs before incision and drainage are done.

As a general rule it is well to leave superficial infections alone and watch and see if they dry up under simple topical therapy. The time of healing will be slower but it will be more comfortable for the patient and it will be a further step in preventing the child from becoming over-concerned about the comedonal development. Systemic therapy in the form of antibiotics may be used for the acute developing lesion with cellulitis. The question of antibiotics and their application will be discussed later.

The preparations used for treatment of the superficial infections may be the mixture of sulfur, salicylic acid or resorcinol, etc. Ordinarily, colored preparations are preferred, since they have some cosmetically covering tendencies. All the medicated preparations used in the treatment of acne may dry and irritate but fortunately this reaction is not

too common on the greasy type of skin. If the condition becomes progressive and the topical applications are used much more extensively, then risk of developing a dermatitis is proportionately increased. This irritation is more apt to occur first about the eyelids, corners of the mouth, and neck. It is well to recognize these early signs of irritation and to stop the medication and use a simple bland cream if necessary.

As the patient with acne gets older and the incidence and severity of pustulation become marked and, in the girl, become related to menstruation, treatment should be more regular, more standardized, more vigorous and under more frequent observation by the physician.

DIETARY FACTORS

The difficulty of determining the exact role of dietary factors has been emphasized repeatedly. A greater knowledge of the physiology of sebum and the true endocrine influence of acne will help us in the future to determine the exact influence of diet. Because of the frequency of the relationship of ingestion of chocolate to the occurrence of a flareup, we have been attempting to study in a critical fashion, as regards the accuracy of this observation, the type of chocolate, the influences of lipoidal materials, etc. Our studies are still in a preliminary phase. We can only state that when the patient is certain about the aggravating influence of chocolate, then chocolate should be eliminated for at least three months.

Indulgence in large amounts of salt and especially iodides should be prohibited. The exact role of iodized salt in the production of acne cannot be determined as yet from our own studies, but only in the severe forms is it our principle to eliminate iodized salt. There is no proof at present that average intakes of carbohydrates or fats have any influence on the development of acne. We ask simply for a balanced diet. For those who believe that dietary factors are important, a trial period of a type of diet is suggested in an attempt to convince both doctor and patient that diet is not an important feature in the therapeutic regimen of acne.

For the systemic phase of therapy, endocrine preparations are still preferred for the older individual. Vitamin A should be continued in large doses and, in girls, especially in the premenstrual period. The dosage schedule is approximately 100,000 units a day, with the dose doubled in the week before the periods. No toxic reactions have been observed from such dosage levels of vitamin A in this older age group. If it can be determined that the organisms present in the secondary infected lesions are sensitive to antibiotics, then these may be employed with due recognition that they will not cure the acne, but will only help the secondary infection.

ULTRAVIOLET THERAPY

Local cleansing and drying measures are continued now in a more regular fashion. The older individual has the responsibility of carrying out these directions by himself or herself. Regular daily ultraviolet therapy may be had at home. This should be supervised by the parent until the youth gets old enough to do it himself. Ultraviolet therapy should be in doses of suberythema and should be discontinued in the presence of irritation. Efforts should be made to prevent the child from going to sleep under the ultraviolet lamp. In the seborrheic patient, therapy with ultraviolet has a good effect. X-ray therapy is reserved for the older youth, for the nodulocystic phases; this form of treatment should be given only by the experienced specialist, and then only as part of a planned regimen, not as the sole therapeutic measure.

TOPICAL TREATMENT

The role of topical treatment is even more important now, because the individual is highly concerned and has become completely "skin conscious." For this reason, again those preparations which are colored are preferred, for emotional factors can certainly aggravate acne. Covering the lesions is a part of the program of adjustment of the patient to the acne. These preparations are available as various sulfur and resorcinol products. They should be given only in prescription form so that their effect can be watched. When the skin is dry and acne is still present, then creamy types of vehicles may be used with caution. It is best for the practitioner to get a few preparations and learn how to use them and learn their value and their distinct limitations. The patient must learn to keep from picking or opening the lesions or even keeping them covered with the hands in an effort to conceal them.

NODULOCYSTIC LESIONS

As the acne becomes more severe and deep nodulocystic lesions appear, an effort should be made to treat the condition clinically as a systemic infection. The patient should be studied carefully to determine the existence of any factors such as anemia, tuberculosis, sinusitis, menstrual irregularities, etc. The pus from the nodulocystic lesions should be examined and the organisms isolated should be studied for their sensitivity to the antibiotics and the possibility of the use of an autogenous vaccine. It is our feeling that when all organisms, including the so-called *C. acneii,* are isolated, the results of prolonged vaccine therapy are better than with the use of stock measures of various types. It is well in these more severe forms, especially in older individuals, to consider any type of therapy which may cut down the secretion of

sebum. Estrogen should be used with due regard to its reactions, effect on menstrual periods, male breasts, etc.

We are also studying a number of investigative procedures in an attempt to minimize the extensive scarring that occurs in these individuals. None of these measures can be recommended as yet for general use.

In the local treatment of this condition, the lesions should be drained, especially as they continue to spread. Drainage should be done at the infected portion of the lesions and the lesion should be incised widely and packed if necessary. Our attempts at local infiltration with antibiotics have not been too successful. When these severe nodular, or so-called acne conglobata phases occur, consultation with the plastic surgeon should be done in an attempt to reduce the severity of these reactions. However, plastic surgery for acne is still in an investigative phase including procedures for the reduction in intensity of scarring. The practitioner should not attempt any of these technics himself. The real treatment of these scarred lesions of acne is in the early treatment in their developmental and active phase.

The deep type of acne will not disappear as the patient gets older and goes into the "golden twenties"; therefore, active treatment should be continued until it is shown that no new lesions develop.

CONCLUSIONS

There are many facts lacking in the understanding of the background of acne, and many fancies, fortunately for the most part not dangerous, are favored in practice. However, the local treatment is important, and it is the practitioner who can apply the principles of topical therapy in the early phases. It is the practitioner also, with his opportunities for the continued observations of the family group, who can treat the early developments of acne when so-called preventive therapy can accomplish results. Moreover, it is the practitioner who can study the backgrounds of the fluctuations of the course of acne. The principles of a practical program of cleansing, drying and antiseptic measures, and some recommendations for general measures are given for the development of acne throughout the various age periods.

Treatment of Hypopituitarism

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In clinical practice one encounters hypopituitarism in adults chiefly in cases of chromophobe pituitary tumor. Simmonds' disease, which is hypopituitarism resulting from thrombosis or infarction of the pituitary arteries, and Sheehan's disease, which is identical except that it occurs postpartum from excessive hemorrhage and shock, are both relatively rare. The actual treatment of the tumor itself rarely has any beneficial effect on the already impaired pituitary function and for this reason will not be discussed in this paper.

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Since the anterior pituitary provides tropic hormones for the thyroid, adrenal cortices and the gonads in the adult, deficiencies of these glands comprise the background for signs and symptoms. Before and during adolescence deficiency of growth hormone contributes to the clinical syndrome by retardation of growth rate.

Ideally, a mixture of thyrotropic, adrenotropic and gonadotropic hormones should provide adequate substitution therapy for the deficient anterior pituitary gland, although prolonged deficiencies of these tropic hormones may lead to degenerative changes in the respective target glands, thus reducing the likelihood of adequate response on the part of these organs and necessitating substitution of the hormones of the secondary glands themselves. Adrenotropic (ACTH) hormone is available commercially, as well as chorionic gonadotropin, which is a fairly good substitute for the luteinizing (LH) or interstitial cell stimulating (ICSH) hormone. Thyrotropic and pure follicle stimulating hormone

(FSH) are not commercially available. To date no one to my knowledge has administered these three groups of hormones simultaneously to a patient with hypopituitarism. It is entirely possible that the result would be eminently successful, including spermatogenesis in properly selected cases. Expense alone precludes such a trial except in those patients with unlimited incomes.

Reasonable health can be restored in some patients without the use of pituitary hormones. Before the availability of ACTH or cortisone, for a period of over 10 or 12 years testosterone and desoxycorticosterone acetate have been administered by pellet implantation in both women and men.* Testosterone has an anabolic effect in both men and women, provides greater endurance, has a favorable but limited effect on hemoglobin and red cell count and restores pubic and some axillary hair, which has definite psychologic value. Desoxycorticosterone elevates the blood pressure and appears to add to the improved sense of well-being, as it does in Addison's disease. On this regimen one patient with Sheehan's disease has been observed to have a complete cessation of hypoglycemic reactions which she had experienced prior to receiving therapy.

Desiccated thyroid may be administered orally after the therapy described has been in effect for a month or more. Doses of 1 or 2 gr. may then be tolerated, whereas without the protective effect of testosterone and desoxycorticosterone fairly rapid weight loss, weakness, tachycardia or, even more important, the precipitation of an acute adrenal crisis, may be produced by desiccated thyroid.

Usually 4 or 6 pellets of testosterone (75 mg. each) are implanted every three to four months. Two pellets (75 mg. each) of desoxycorticosterone are inserted with the initial implantation of testosterone but do not require replenishment for six months or longer. Loss of weight, increasing fatigability and decreasing blood pressure are usually present when the desoxycorticosterone pellets have been completely absorbed. I have implanted all pellets in the subcutaneous tissue of the anterior surface of the thigh because this area is accessible and it is more convenient for the patient to palpate the pellets and determine when they are almost gone.

ACTH has been used in 4 patients with proved hypopituitarism, with excellent results in 3. One woman, 60 years of age, with rheumatoid arthritis who had been maintained on testosterone and desoxycorticosterone for over a year without much improvement in arthritis was then given ACTH in doses up to 80 mg. a day during the first week, with a gradual reduction to 20 mg. a day during the next few weeks and finally 10 mg. every other day for four months. She has had as near a complete restoration of health as would seem possible. Pellets of testosterone and desoxycorticosterone acetate were reimplanted after several weeks of ACTH therapy. During the six months of treatment there has been a gain of 20 pounds in weight without evidence of fluid retention or Cushing-like signs. ACTH therapy has been discontinued for three months without a relapse of the arthritis.

A 60-year-old man with hypopituitarism due to a chromophobe tumor (which had also produced bitemporal hemianopsia and had been successfully treated with roentgen therapy 12 years before) had been receiving pellet implantations about every three months for eight years. He had chosen this form of therapy in preference to intramuscular injection, oral or buccal administration. On a total of 25 mg. of ACTH daily given in divided doses two times a day there has been such an improvement in energy and decrease in fatigability that he has a renewed interest in his business, expanding it for the first time in years. He has been on this dosage for three months without complications. Part of his improvement may be credited to a mild euphoria. Whenever the dose has been reduced, the effect is readily noticed and the preceding dosage has been resumed. Implantation of testosterone pellets has been continued.

The third patient with objective hypopituitarism, a man of 57 years, almost totally blind from pituitary tumor, has received marked subjective improvement as regards lack of energy and aching joints on ACTH and believes that 10 mg. every other day has maintained this improvement over a period of three months.

The fourth patient, a man of 27 years, whom we have observed over a period of 10 years and have given the aforementioned regimen irregularly, was given a trial of 40 mg. of ACTH daily for a week. Although the eosinophil response indicated responsive adrenal cortices, no noticeable effect was noted by the patient nor was any change observed clinically. ACTH was given twice daily to this patient instead of every six hours, which may have been the explanation of failure to improve, but insufficient dosage may also have contributed. The administration of desiccated thyroid before giving ACTH is said to enhance the effect of the latter, but should be given with caution, as stated.[1]

In refractory cases such as the fourth case may prove to be, cortisone should be tried. Initial doses of 100 mg. a day should suffice. We found cortisone to be effective orally and this was confirmed in a communication from Dr. Carlisle* of Merck & Co. To date it appears equally as effective, dose for dose, as when given parenterally. The suspension may be flavored with fruit juice or placed in gelatin capsules. Tablets are now available.

In view of its apparent effectiveness by the oral

*The author is indebted to the Schering Corporation for the generous supply of pellets used in some of the cases.

*To whom the author is grateful for a generous supply of cortisone acetate in tablet form.

route there would appear to be little need for pellets of cortisone. We have tried desoxycorticosterone by the buccal route in hypopituitarism without effect on blood pressure or clinical findings. Perhaps larger swallowed doses might be as effective as pellets and may well have been tried by others.

The most practical therapy of panhypopituitarism, therefore, would appear to consist of substituting those hormones of the secondary endocrine glands rather than the tropic hormones of the pituitary, with the exception of ACTH. While cortisone may not accomplish all that ACTH therapy does, it may suffice for satisfactory results. In some cases of hypopituitarism in males, oral or buccal administration of testosterone is satisfactory. The response to oral therapy, however, is less satisfactory than intramuscular or pellet administration if one can accept the patient's verdict. Administration of desoxycorticosterone has been used chiefly in the more severe cases of hypopituitarism.

Amenorrhea occurs in females with enlarged sellas presumably due to chromophobe tumor who do not always have evidence of panhypopituitarism. Examination of the vaginal smear in panhypopituitarism shows absence of glycogen in the epithelium (Mack technic),[2] whereas if glycogen is present it is unlikely that significant panhypopituitarism is present.

Administration of estrogen will glycogenize the vaginal smear in panhypopituitarism and bleeding may occur upon withdrawal or upon administration of progesterone, parenterally or buccally. If the vaginal smear is glycogenized before therapy, progesterone alone may induce flowing. Estrogen-progesterone therapy may be used in panhypopituitarism in females under 40 years of age for whatever psychologic value may be derived.

In males, spermatogenesis is possible with administration of chorionic gonadotropin, and I have observed 1 case in which spermatogenesis occurred in a man of 38 with the administration of chorionic gonadotropins and methyltestosterone initially; the spermatogenesis was maintained by the latter alone.[3]

If chorionic gonadotropin is to be used with hope of spermatogenesis in the younger male with hypopituitarism, its effectiveness will be shown in much the same way as upon administering testosterone. Since chorionic gonadotropin stimulates Leydig cell formation and function, growth of pubic hair should occur, libido and erections should be increased as well as the general anabolic effects of testosterone. Continued use for periods of over a year are impractical so that one usually resorts to testosterone. In an all-out attempt to render the male hypopituitary patient fertile, administration of chorionic gonadotropin (and FSH if available, minimum 1,000 units), ACTH, 10 to 40 mg. and desiccated thyroid, 1 to 2 gr. could be tried daily.

If fertility is not a problem, the therapy may be carried out according to the following plans, depending on the severity of the disease, their effectiveness and cost of the various products. Desiccated thyroid may be used after the initiation of treatment and continued if benefit is derived.

1. ORAL OR BUCCAL ROUTE

(a) Testosterone (free or methyltestosterone)—30 to 50 mg. daily.

(b) With or without cortisone daily—20 to 100 mg. daily.

2. PELLETS AND CORTISONE

(a) Testosterone (75 mg.)—4 to 6 every two to four months.

(b) Desoxycorticosterone (75 mg.)—1 to 2 every 6 to 12 months.

(c) Cortisone (oral or parenteral)—25 to 100 mg. daily.

3. TESTOSTERONE AND ACTH

(a) Testosterone pellets as above, or

(b) Oral testosterone as above, or

(c) Parenteral testosterone (free or propionate)—50 mg. every other day.

(d) ACTH (may be tried alone in these doses)—5 to 25 mg. daily for maintenance.

For acute adrenal insufficiency of panhypopituitarism, ACTH may be given intravenously in doses of 10 to 50 mg. along with 500 to 1000 cc. of saline solution administered slowly or parenterally in doses up to 100 mg. every four hours depending on response, but for immediate action adrenal cortical extract is preferable along with intravenous glucose, saline and antibiotics if indicated. When ACTH is employed for any length of time (after recovery from the acute state) in doses over 40 mg. daily, the usual precautions against potassium depletion and salt retention should be observed by administering potassium on the one hand and restricting salt on the other.

REFERENCES

1 ACTH; General Principles to be Considered and Directions for Using. Armour Laboratories, 1950, p. 37.

2. Jones, H. W., Jr., and Hurxthal, L. M.: The iodine vapor stained vaginal smear: its use in office practice. J. Clin. Endocrinol. (In press.)

3. Hurxthal, L. M., Bruns, H. J., and Musulin, N.: Development of spermatogenesis in hypogonadism. J. Clin. Endocrinol. 9:1245-1258 (December) 1949.

Pediatrics

IN GENERAL PRACTICE

For general practitioners, in whose practice is included a major proportion of the medical management of infants and children, and for the specializing pediatrician as well, POSTGRADUATE MEDICINE *presents this special regular department devoted to brief discussions by recognized authorities on their preferred methods of the treatment and management of diseases and problems of infancy and childhood.*

Disturbances of Growth

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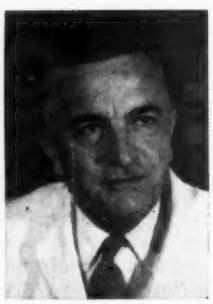

JOHNSTON

In an analysis of the presenting complaints of 2000 infants and children brought to an active clinic, 7 per cent related to an abnormality of growth and development. As might be expected, the complaint was unjustified in a fairly large percentage of these, the parents failing to appreciate the variability within the normal range. Commonly, a comparison of their child with a neighbor's of similar age led to the concern.

The assessment of the normalcy of growth and development poses some very real problems that lack a simple clinical solution. The use of height and weight as over-all measures of progress in growth has a limited value. Because such measures derive from averages of cross sectional material, unjustified concern results from failure to view them with the deviations of the normal frequency curve in mind. Their value increases when they are used as points in a curve of growth, but this requires serial measurements at significant time intervals. Wetzel's grid or the Iowa Growth Charts make a practical application of this type of charting and represent an improvement over the isolated measurement. However, except when defects are extreme, they do not reflect variations in the composition of growth that should concern the clinician. With balance studies, we have recorded periods of as long as six months when huge amounts of nitrogen and calcium were being added to a convalescent body while the weight curve remained a plateau, and conversely we have recorded equally long periods of weight gain accompanied by nitrogen and calcium loss (Figure 1). Much of this information can be gained by inference from a carefully taken dietary history and a knowledge of the varying requirements for growth at its different levels.

When the problem of growth retardation can be accepted as real, however, the approach to its solution involves a consideration of the following major factors influencing it: heredity, diet, infection, congenital defects in major systems—central nervous, cardiorespiratory, genitourinary, gastrointestinal, muscular and osseous—and the endocrine glands.

HEREDITY

An isolated observation of height and weight that results in a child's appearing much smaller or larger than his chronologic peers might be dismissed as due to an inherited factor, but it is still true that a pathologic departure from normal would be evident when two determinations are made at significant intervals. For example, in one case I

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was willing to accept as familial a child's smallness and to reassure the parents until on subsequent observations it was noted that her progress in height and weight plotted against time showed her to be advancing at a pathologically slow rate. It was not until two years later that signs of increased intracranial pressure appeared which led ultimately to the diagnosis of craniopharyngioma. Comparing this child's weight with that of girls of similar height gave no helpful information, but plotting progress in both directions against time, as is done on the right hand side of the Wetzel grid, gave a picture of dwarfism (Figure 2).

DIET

The extent to which diet plays a role in growth disturbances is rather heavily conditioned by the economic circumstances. In analyzing growth failure in a clinic for indigents, the food factor is of major importance. In a study of a group of children with a complaint of malnutrition from the middle upper economic strata, it was of far less significance and in 86 per cent of those it was much more likely that a disease process would be found interfering with the utilization of food. The composition of growth will of course be heavily influenced by diet, and a careful record, such as a diet diary for a week, contributes importantly to an understanding of this at critical periods such as adolescence. While at periods of more stable growth a fairly wide latitude in the intake of protein can be tolerated without ill effect, the exact fulfillment of the requirement becomes much more important during the sharply accelerated and decelerated phases of growth that precede and follow menarche in the girl.

The slipped epiphysis of the adolescent occurs quite consistently in the accelerated phase of adolescent growth and seems to be associated with a disproportionately rapid gain in weight. Studies on seven of these children show that while they were gaining well in weight they were storing calcium inadequately, and logical management of the obese adolescent calls for a very rigid fulfillment of the calcium and vitamin D requirement, while at the same time the caloric intake is being restricted at the expense of carbohydrate and fat. Calcification would appear to be a function not only of intake but also of growth speed. Data are reproduced showing the calcium and nitrogen balance for five of these children, three with and without vitamin D, one with thyroid and one with testosterone (Figure 3). While the low or negative balances in the control period in these children were undoubtedly due in part to bed rest and surgical intervention, such balances can be improved by giving added vitamin D but are made worse by thyroid and testosterone.

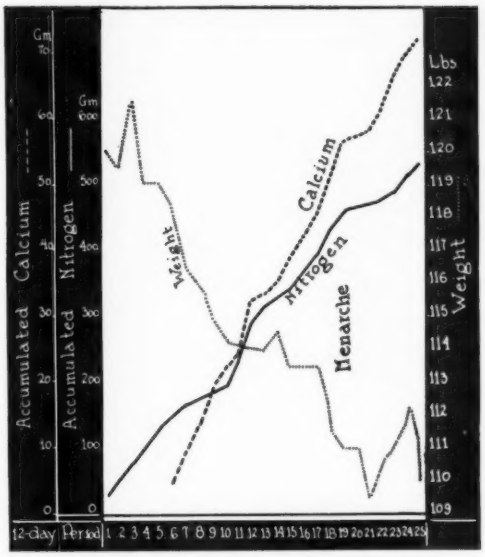

FIGURE 1. Cumulative nitrogen and calcium balances, showing the consistent accumulation of nitrogen and calcium to be compatible with a steadily declining weight curve.

(From Johnston, J. A.: Am. J. Dis. Child. 59:287, 1940.)

INFECTION

It is common to find that the food intake is adequate and yet that there is a failure of weight gain in the child with chronically infected tonsils. The effect of a focal infection on growth is somewhat obscure but must involve a toxic destruction of protein independent of fever. Figure 4 shows results of a study of the retention of nitrogen and calcium before and after a tonsillectomy as an example of the effect on the nutritional state of removing a focus of infection. This study was stimulated in part by a desire to check the nature of the weight gain that followed tonsillectomy. In the sense that this gain includes improved storage of nitrogen and calcium, it can be considered desirable.

CONGENITAL DEFECTS IN MAJOR SYSTEMS

True retardation of growth is a component of any serious defect in the major systems—central nervous, cardiorespiratory, genitourinary, gastrointestinal. Thus, it is common to refer to "renal infantilism," "intestinal infantilism," "cardiac infantilism," etc. In the first year of life, particularly when the problem of slow growth is present, these are the first items to investigate. As typical of this situation, a five months old infant was seen be-

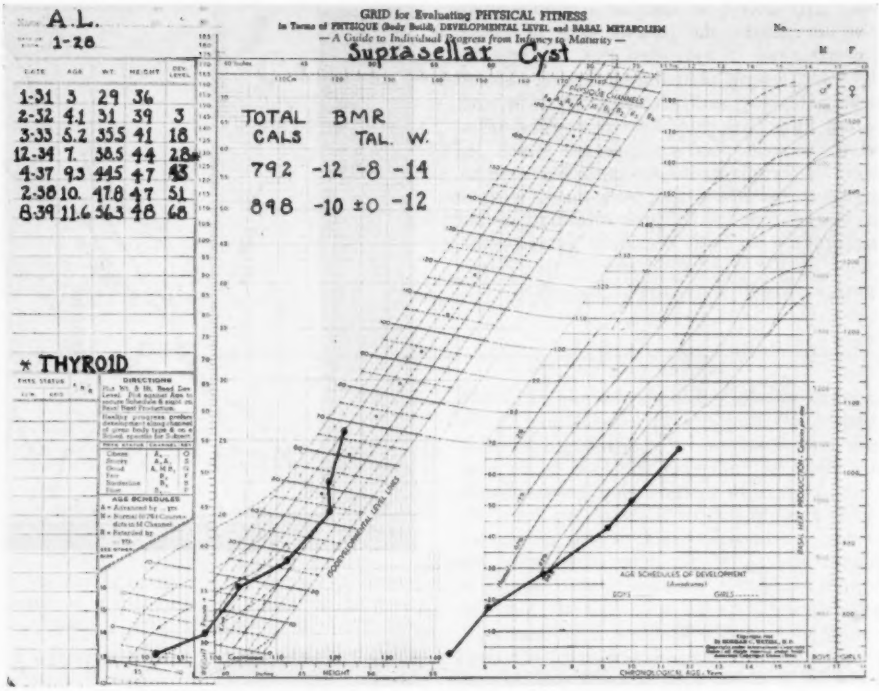

FIGURE 2. In terms of weight for a given height, this child did not depart greatly from the normal but it was quite evident from the right hand side of the chart that the developmental level resultant of growth in two directions was definitely dwarfish.

(Reproduced from Grulee and Eley: "The Child in Health and Disease." Williams & Wilkins Co., publishers.)

cause of failure to gain in height or weight in spite of an excellent feeding and perfect home environmental circumstances. When the usual physical examination revealed no obvious cause for this, renal studies were clearly indicated. An intravenous pyelogram revealed a polycystic kidney.

CELIAC DISEASE

The intestinal infantilism produced in this disorder is evidenced in slow growth in weight before the overt manifestations of digestive difficulty become apparent; in fact, the writer believes that this disturbance usually has a dual etiology. The factors associated with abnormal stools have been listed as infectious, allergic and emotional, and yet none of these in itself commonly causes intolerance to starch and fat. In a series of nearly 40 of these children, 26 showed manifestations of thyroid deficiency and failure of normal growth preceding the appearance of stools characteristic of starch intolerance or indigestion. Eighteen showed infection, usually of the adenoids. In 11 there was a strong psychogenic element involved in their management by oversolicitous parents or, at the other extreme, an absence of normal maternal relations. Allergy seemed to play a role in only two cases. All four of these elements should be looked for in the child with chronic intestinal indigestion, but the finding of infection cannot be accepted as the sole cause of the disease unless it is also associated with and superimposed on a metabolic defect, such as would result from a thyroid deficiency (Figure 5). It was possible to determine calcium balances on two of these children and to show that while the stools could be controlled by the conventional high protein diet, calcium was still not absorbed until thyroid was given. The amounts required for this correction are as small as might be expected when the need for this hormone exists, namely ¼ gr. U.S.P. In fact, one of the few good tests for thyroid deficiency in the first year is the sensitivity to its administration.

ENDOCRINE BASIS FOR GROWTH FAILURE

Pituitary—True pituitary dwarfism is seldom

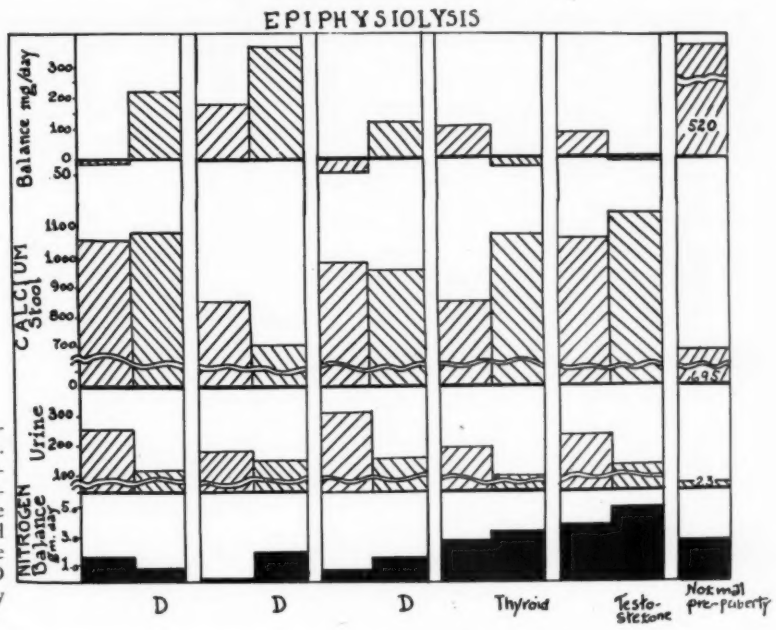

FIGURE 3. CALCIUM BALANCE IN EPIPHYSIOLYSIS. The low or negative balances in the control periods are in part referable to bed rest and surgical intervention. They can be improved with vitamin D but are made worse by thyroid and testosterone.

uncomplicated by another deficiency since normal thyroid function depends upon the thyrotropic hormone. We have as yet no useful preparation for the management of pituitary dwarfism save the recognition of tumors and their surgical removal. The growth hormone in the preparation ANTUITRIN G® does cause nitrogen storage but quickly provokes antihormones and has no effect after a few weeks.

Thyroid deficiency—The degree of hypothyroidism severe enough to produce a cretin is considered too obvious a problem to be discussed here. It is never evident at birth, manifesting itself about two months after the effect of maternal thyroid has been lost. While the cretin state is generally appreciated, lesser grades of thyroid deficiency are commonly ignored, manifesting themselves chiefly by a failure to grow in height and weight at a normal rate, and ultimately by such overt signs of bowel dysfunction as the celiac syndrome. In the presence of an adequate diet and good care, and in the absence of either chronic infection or a congenital defect in one of the major systems, evidence of thyroid deficiency should be sought as a cause for slow growth. The means usually employed to confirm the impression include assessment of the skeletal age, determination of the alkaline phosphatase, carotene, cholesterol, glucose tolerance curve, uptake of radioactive iodine, and, in the older child, determination of the basal metabolic rate. A final observation to be made is the response to therapy.

In the year old infant, the normal variation in bone age is great enough to make this assessment difficult to evaluate. We employ the standards suggested by Vogt and Vickers which have the usefulness of recognizing the departures from the statistical mean. Alkaline phosphatase levels parallel the speed of growth. Levels under 4 have been noted in the untreated cretin. The level of cholesterol has been of little use in our experience, though a sharp rise following the withdrawal of treatment is said to occur. It takes, however, between seven and nine weeks for the effect of thyroid to wear off.

Elevated carotenes are said to characterize the hypothyroid state but can scarcely be expected to do so if there is also the complication of steatorrhea which frequently occurs. A practical clinical use of the uptake of radioactive iodine is not yet available. It is our current feeling that the single reading 24 hours after ingestion as compared with the previous day's base line may be the most useful way to employ this measure. It should be emphasized that the dose required to correct thyroid deficiency in the infant and small child is very small. One of the real indications for the need for thyroid is the sensitivity of response to it. We usually begin with ¼ gr. U.S P. and cautiously increase the dosage. Even in cases of fully developed cretinism 1½ gr. has usually proved to be sufficient. It should be recalled that excessive amounts result in negative calcium balances whereas sufficient amounts convert a negative balance to a positive one.

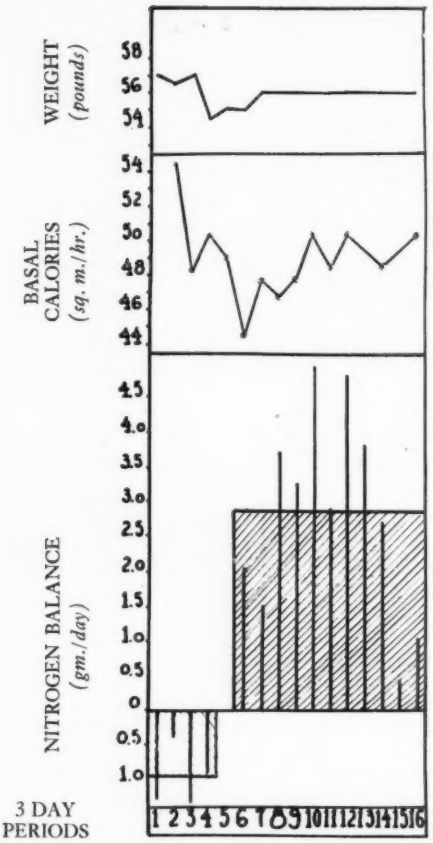

FIGURE 4. The effect of the removal of infected tonsils on the retention of nitrogen. Patient was a 9 year old boy; height, 50 inches; established weight, 58 pounds; tonsillectomy, first day, fifth period.

(From Johnston, J. A.: J. Pediat. 12:563, 1938.)

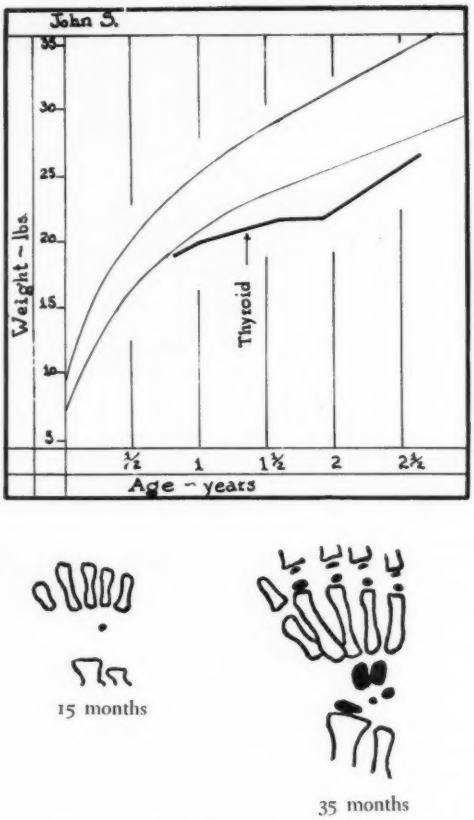

FIGURE 5. Patient's history suggested thyroid deficiency at 10 months of age; celiac symptoms appeared at 14 months of age. RBC, 3.8 million; Hbg., 10.9 gm.; glucose tolerance, 72, 76, 74, 54 mg. per 100 cc.; A—absorption, 31.9 micrograms; carotene, 180 micrograms.

(From Johnston, J. A.: J. Pediat. 35:1, 1949.)

Testosterone—Talbot et al. feel that there is a place for this hormone in promoting growth when emotional and nutritional factors and hypothyroidism have been excluded as a cause for retardation, especially in retarded boys of adolescent age. It cannot yet be said, they warn, that such hormonal therapy is free from permanently harmful effects on testicular function. In our balance studies with this hormone, increased retention of nitrogen was accompanied by a fall in the storage of calcium and, with the doses we used, undesirable stimulation of the sex glands. This may not prove to be true of the newer preparation, mestenediol, but our experience with this is too limited as yet.

Adrenal—Adrenal insufficiency is of course incompatible with growth but the other manifestations of this defect overshadow this strikingly. Rarely will a consideration of this hormone arise when the presenting complaint is growth failure alone.

THE OBESE ADOLESCENT AND HYPOGENITALISM IN THE MALE

This is included as a growth disturbance because of the widespread feeling that there is some defect in genital development associated with the obesity so commonly seen in the adolescent. Part of the reason for assuming an endocrine disturbance has been the misinterpretation of basal metabolic determinations done on such children. Calculated on the conventional surface standards, the

rates are of course reported as low. This basis, however, gives misleading results when there is an excessive amount of fat.

A truer interpretation of the metabolic rates results when the standard predicted from the Wetzel developmental level is used in which excessive fat does not contribute proportionately to raise the level. A height standard may also be used, and when the calculations from this standard are compared with those on a surface area basis, the correction is of the magnitude of 20 per cent. Not only is thyroid not helpful for these children; it is actually harmful, resulting in the demineralization that results from excessive thyroid.

Most obese boys, in whom the question of adequacy of genital development is raised by parents, have normal genitals which are merely obscured by a fat pad, and can be expected to appear more normal after weight reduction by diet. True infantilism should be considered in the boy of 17 whose testes have an actual mass equivalent of less than a volume of 2 cc. and at that time some thought could reasonably be given to specific treatment with chorionic gonadotropin or testosterone.

REFERENCES

1. Johnston, J. A.: Factors influencing retention of nitrogen and calcium in the growth period. III: Puberty in the normal girl and in the girl with minimal reinfection tuberculosis. Am. J. Dis. Child. 59:287 (February) 1940.
2. Johnston, J. A.: Physical growth and development. In: Grulee, C. and Eley, C.: The Child in Health and Disease. 1948, The Williams & Wilkins Company, Baltimore.
3. Johnston, J. A. and Maroney, J. W.: Focal infection and metabolism; effect of removal of tonsils and adenoids on nitrogen balance and the basal metabolism. J. Pediat. 12:563-570 (May) 1938.
4. Johnston, J. A. and Howard, P. J.: The celiac syndrome; factors influencing its development with particular reference to hypothyroidism as contributing cause. J. Pediat. 35:1 (July) 1949.
5. Vogt, E. C. and Vickers, V. S.: Osseous growth and development. Radiology 31:441 (October) 1938.
6. Talbot, N., Sobel, E. H., Burke, B. S., Lindemann, E. and Kaufman, S. B.: Dwarfism in healthy children; its possible relation to nutritional and endocrine disturbances. New England J. Med. 236:783 (May) 1947.

Treatment of Whooping Cough

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BRADFORD

Between 1941 and 1945 approximately 13,000 deaths from whooping cough occurred among persons under 15 years of age in the United States. Ninety-six per cent of these deaths were in children under 5 years of age. About 70 per cent of the deaths from pertussis now occur during the first year of life and 40 per cent of these are in infants under 5 months of age. The usual hospital mortality rate is between 5 and 10 per cent.

Although the general mortality rate has gradually decreased since 1935 there has been, during this period, an increase in the death rate of children under 1 year of age, and a corresponding decrease in the percentage of deaths among those over 1 year of age. This finding has been explained in part by the beneficial effect of vaccine given to older infants and children and by the more effective administration of the newer therapeutic agents to the older patient, particularly in the treatment of pneumonia which is an important factor in the cause of death.

According to Dauer the highest mortality rate now exists in rural rather than in urban areas and depends in part upon the relative lack of adequate hospital facilities for the proper management of the more serious types of infection.

Early diagnosis and isolation are important for they give protection to the patient against superimposed infections and prevent the spread of pertussis to others. Bed rest is desirable during the early stage of the disease. Constant room temperature is preferable to extreme changes which provoke coughing. Smoke, dust and excitement should be avoided.

When vomiting is excessive, small frequent feedings are indicated. A diet adequate in calories and vitamins should be offered.

There is no other disease in which good nursing care is more essential. The handling of severe paroxysms with cyanotic spells and the feeding of such patients constitute a nursing problem which demands the services of an experienced individual. Obviously such service is frequently found only in communicable disease hospitals. Oxygen is perhaps the most important single therapeutic agent for cases with convulsions (about 8 per cent of hospitalized patients) and for those with dyspnea with or without cyanosis.

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Strangling caused by the accumulation of mucus in the bronchial tree may be relieved by aspiration with a soft rubber catheter. This, also, is most effectively done by an experienced nurse. A moderate amount of steam inhalation may be useful in certain cases.

Sedatives should not be given excessively, for they abolish the cough reflex which in time leads to retention of the bronchial secretions.

DRUGS

The following drugs are useful (doses given for a 5-year-old child):

Phenobarbital .....30 mg. (½ gr.)
Codeine sulfate .....15 mg. (¼ gr.)
Paregoric ..... 2 cc. (30 minims)
Phenobarbital sodium ..30 mg. (½ gr.) intramuscularly

The rectal instillation of 4 cc. of ether in 15 cc. of olive oil every eight hours as necessary is effective for severe paroxysms. Convulsions are often relieved by the prompt administration of oxygen and sometimes by the performance of a lumbar puncture. Sulfadiazine is effective against *Hemophilus pertussis* in vitro and in vivo. It is also useful against certain complicating pyogenic organisms. The dose is 0.1 gm. per kilogram of body weight (½ to 1 gr. per pound) per day.

There is no one antibiotic which may now be said to be the one of choice. Streptomycin, aureomycin, CHLOROMYCETIN® and terramycin are all effective against *H. pertussis* in vitro and each protects mice against the experimental disease. There is also some evidence of the favorable action of each against the clinical disease.

In the case of streptomycin the organism may become rapidly resistant. Moreover, the administration of this drug may lead to permanent deafness in certain instances. It should not be used for more than two to four days. The dose is 50 mg. per kilogram of body weight daily in equal doses every four hours.

SERUMS

Human and rabbit antiserums are effective and should be used in all severely ill infants. As a result of the injection of these antiserums significant humoral antibody titers against the organism can be readily demonstrated.

Hyperimmune human serum may be injected in from 20 to 40 cc. amounts either intramuscularly or intravenously at 48 hour intervals for two or three injections.

Gamma globulin prepared from hyperimmune human serum (hypertussis) may be injected intramuscularly in 2.5 cc. doses every 48 hours for three or four injections.

Antipertussis rabbit serum possesses a much greater content of antibody per volume than does either of the two human serums. It is injected in doses of from 2 to 10 cc. every 48 hours for two or three injections. Preliminary tests for sensitivity should be made before injection of this serum. It is particularly effective in combination with sulfadiazine.

Any one of these three serums should be used prophylactically for the passive protection of exposed infants who have not had the benefit of active immunization.

REFERENCES

1. BELL, J. A., PITTMAN, M. and OLSON, B. J.: Pertussis and aureomycin. Pub. Health Rep. 64:589, 1949.
2. BRADFORD, W. L. and DAY, E.: The action of aureomycin, of polymyxin B and of streptomycin in experimental murine pertussis. J. Pediat. 35:330, 1949.
3. BRADFORD, W. L.: Recent contributions to the diagnosis and treatment of pertussis. New York State J. Med. 49:397, 1949.
4. GORDON, V. H. and ALMADEN, P. J.: Streptomycin therapy for pertussis. J. Pediat. 34:279, 1949.
5. KAPLAN, M. Z. and LARSON, J. B.: The use of rabbit serum in the treatment and prophylaxis of whooping cough. Kentucky M. J. 46:292, 1948.
6. KOHN, J. L. and FISCHER, A. E.: Management of whooping cough with special reference to infants. Am. J. Dis. Child. 73:663, 1947.
7. MILLER, W. J. and ROSS, J. E.: Aureomycin in the treatment of pertussis. J. Pediat. 37:307, 1950.
8. PAYNE, E. H., LEVY, M., ZAMORA, G. M., VILARROEL, S. and CANELAS, E. A.: Pertussis treated with chloramphenicol. J.A.M.A. 141:1298, 1949.

"THE PATIENT AND THE *PATIENT*"
(BY THOMAS C. STEVENSON, M.D., MENLO PARK, CALIFORNIA)
(Shown at American Physicians' Art Association, 1950)

EDITORIALS

Postgraduate Medicine FOR THE CONTINUING EDUCATION OF THE PRACTICING PHYSICIAN

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THE PHILOSOPHY OF REHABILITATION

A FIRST and then a second World War made us realize the full importance of reaching and maintaining optimum physical and mental efficiency, not only in our armed forces but throughout the production line of industry. To do so was essential if we were to achieve victory over our enemies and maintain economic stability on our home front.

Accordingly it was imperative that the casualties of mobilization and battle, and those of industry and disease, be returned to duty with maximum effectiveness in the shortest possible time.

The dynamic and untiring efforts of Dr. Howard A. Rusk, Dr. Harry D. Kruse and many others have quickened the interest of business and industry in rehabilitation and its relationship to our future economy. Mellon Institute, the Baruch Committee, and hundreds of other enthusiastic organizations and individuals are carrying the ideals and objectives of rehabilitation to the far corners of our country.

It is my opinion that every person in any of these special groups, including the family physician, should regard himself, in the true sense of the word, as a rehabilitationist. If we are to produce maximum comeback after accident, illness or mental handicap, it is imperative that every person having a part in care and convalescence, from his very first contact with the patient to his last, consider and plan the patient's early return to economic independence.

In addition to his medical responsibility, there is also a sociologic responsibility that every physician must assume if he is to fulfill his obligation to his patients. It is essential that he appraise his patient's possibilities as a wage earner after he returns to his old job. It is most important from the first to place the patient in the right mental attitude toward his convalescence. He needs more than encouragement; from the beginning he needs something tangible for which to strive.

Of course there are some who, because of the degree of their disability, can never return to anything like their former jobs. At the very beginning every rehabilitationist—doctors, social workers, physical therapists, occupational trainers, and others—must recognize that, if the patient cannot return to his former occupation, his convalescence should be so designed that he may fit himself for some productive line of endeavor and so become an independent, self-respecting citizen.

Teamwork on the part of all who bear the responsibility of rehabilitation is essential for successful fulfillment of their obligation. Each rehabilitationist may do his part well,

but unless, from the beginning of the patient's disability through his convalescence, the over-all picture of his economic and social potentialities is kept in the minds of all who aid in his rehabilitation, the program is incomplete. In other words, if the patient is not prepared for his new position in life, the individual efforts of well wishing rehabilitationists and specialists who have contributed to his improvement have been to a certain extent wasted for want of constant attention to the avowed goal—to return the patient to the community as a self-respecting, economically independent individual.

The job of evaluating the patient's potentialities should start at the beginning of his disability with the family doctor, orthopedic surgeon, or whoever first sees the patient. It is he who should first recognize the patient's potentialities, his future limitations and the extent of his handicap; he should then inaugurate and continue the program of rehabilitation until the patient has returned to an occupation for which he is adequately trained and adapted. The vocational rehabilitationist or guide should be brought into the picture early, before the patient's handicap has become permanently established. The economic loss of a late start toward education and training is tremendous.

The problem of restoring the rapidly increasing number of disabled persons to economic independence as early as possible is becoming acute throughout the nation. Dr. Rusk points to the fact that about 23 million persons in the United States—nearly one-sixth of the population—are handicapped to some extent by disease, accidents, maladjustments or war. Approximately 10½ million persons each year suffer disabling accidents. Of these, nearly a half million incur a permanent disability. Dr. Rusk estimates that over seven million persons in the United States are disabled by diseases of the heart and arteries, and 6,850,000 by orthopedic conditions. Dr. George Deaver and others feel that, unless something is done to restore handicapped persons to vocations best suited to their disabilities and abilities, by 1980 every able-bodied person will be supporting a disabled person. Economists point out that we cannot carry this burden and maintain our present standards of living.

Metropolitan and industrial centers of population with their large rehabilitation and hospital facilities are making great strides not only in starting rehabilitation early but also in carrying through an overall program of restoring the handicapped to a high degree of efficiency and usefulness. It is impossible for the metropolitan centers to serve more than one-tenth or one-twentieth of one per cent of the individuals who need their guidance and service. There is an urgent need for an even greater educational program which will make those far from the great centers recognize their responsibility as rehabilitationists in returning to productivity and usefulness the many handicapped persons in their own communities.

WHAT we need is a philosophy of doing, not stagnating; of producing, not simply using; of independence, not dependency. This is an all-out project in which not only rehabilitationists but every man and woman in the country today should play a part.

Compensation or liability insurance often acts as an obstacle to rehabilitation because the carriers take little or no responsibility beyond paying at a fixed rate for the period of time the patient is unable to work, and then paying a settlement determined by the degree of permanent disability. No thought is given to the patient's future, to change in his occupation nor to his readjustment to a new life. The carrier's objective too often is that of ending the disability payments, not of rehabilitating the patient to a position of usefulness. Personally I feel that the insurance company would be money ahead, and the patient also, if a plan were evolved by which a premium would be paid to the injured worker with less permanent disability and a shorter period of time away from work. Such a scheme would encourage early rehabilitation and great economic saving for industry.

Industry often offers another obstacle by not making a place for these handicapped people. Though they may be liabilities in one position, they can, if rehabilitated, safely perform another type of work. If we are to make full and economical use of our manpower, we must recognize the productive value of handicapped workers.

A phase of rehabilitation to which we must direct particular attention in the next few years is that of our aging population. Census estimates show that 11½ million people in this country are over 65 years of age and that at the present life expectancy we will almost double that number in 30 or 40 years. A recent census report shows, that of 3½ million persons over the age of 65, about one-third are without cash income, and the other two-thirds have an average income of $808.00 a year. Only 10 or 15 per cent have sufficient savings to be financially independent. In another 30 years each able-bodied person, in addition to supporting one disabled person, will probably have to support an aged person as well.

If we are to meet this problem squarely we must first change radically our concept of the value of age. An aggressive, nationwide program must be developed, not only to educate the aging to the necessity of purposeful, productive living, but also to educate the young to a respect for the position, experience and ability of the old. Further, the young must recognize that the time will come when they themselves will have to adjust their productive activity to advancing age and to strive to maintain a high level of physical and mental efficiency throughout their lives.

Our concepts of rehabilitation and the training of the handicapped and of the aging must change with the needs of our economy. We must expand our field of vision to embrace the entire broad horizon of the problem if we are to encompass these needs and if we are to fulfill our obligations as rehabilitationists.

J. E. M. Thomson

(Condensation of a talk presented before the Third Annual Symposium on Orthopedic Appliances at Mellon Institute, Pittsburgh, Pennsylvania.)

TRICHINOSIS

For more than 10 years Dr. S. E. Gould, pathologist to the Eloise Hospital and Infirmary in Eloise, Michigan, has been working on trichinosis. His original thesis,[1] for the degree of master of science in pathology in the University of Michigan, dealt with the incidence of trichinosis among county hospital patients in the Detroit area. The conclusion was that trichinosis is far more common than is ordinarily believed. In a series of 500 unselected consecutive autopsies 93 positive cases of infestation with *Trichinella spiralis* were found. Increasing frequency of infestation was noted in successive decades from the fourth to the eighth inclusive. In none of the 93 patients with trichinosis was the disease recognized clinically; some of the patients had reported rheumatic symptoms and one had, in fact, been diagnosed as having polyneuritis.

Subsequent papers by Dr. Gould have dealt with immunologic reactions, the pathology of trichinosis and new devices for studying the incidence and pathologic changes that occur with this disease. In 1945 he described an effective method for the control of trichinosis in the United States.[2] When the methods of study were more thorough, an incidence as high as 36 per cent had been found, as in a series studied in Cleveland, Ohio.

Trichina infestation comes primarily from eating trichinous pork. The hog becomes infected from eating scraps of uncooked trichinous pork present in garbage. About one and a half per cent of hogs slaughtered are found to be infested. In any given year nearly 90 million hogs are slaughtered and much of the material eaten in the United States, the remainder exported. Each American who eats pork consumes about three servings of trichinous pork each year.

During the past 50 years little progress has been made in the control of trichinosis in the United States. Approximately 70 per cent of American pork is prepared in plants under governmental inspection. However, this does not necessarily prove that the meat

is free from living *trichinae*. A large part of the total American pork supply is open to the danger of carrying live parasites. The consumer may eat pork that has been placed in such meat products as frankfurters, hamburgers, sausages, meat loaf and chop suey. If this has been insufficiently cooked or inadequately processed, the risk of trichinosis is apparent. Dr. Gould feels that sooner or later a method must be adopted for producing a supply of pork free from the danger of causing trichinosis in man. That the condition can be controlled is apparent from the statistics of other countries such as Canada, Poland, Germany and Denmark. Statistics show that in the United States over 14,000 hogs per million were found trichinous compared to only seven hogs per million in Copenhagen.

The measures which have been advocated for the control of trichinosis include destruction of rats, elimination of garbage and of infected material from the feed of hogs, cooking of all garbage fed to hogs, microscopic inspection of pork, proper processing of all pork products which might be eaten without cooking and a campaign of education directed to the public on the necessity of cooking pork and pork products adequately before they are eaten. The principal methods for controlling trichinosis include, therefore, microscopic inspection of pork, cooking of all garbage fed to hogs and processing all pork prior to ultimate sale.

In *Postgraduate Medicine* for April, 1949,[3] Dr. Gould published an article on the diagnosis and treatment of trichinosis presented as a paper before the meeting of the Interstate Postgraduate Medical Association in 1948. In that article and in several others he has reviewed his thesis and has emphasized the necessity for a positive campaign designed to eliminate this unnecessary hazard from the American dietary. The following temperatures maintained for designated periods in the central portions of pork are effective in killing all *trichina* larvae which may be present—namely, from −16.0° F. or −27° C., maintained for 36 hours, to temperatures of −34.6° F. or −37° C. below zero maintained for two minutes. Considerable economy might be effected, Dr. Gould[4] suggests, by subjecting pork products to rapid methods of refrigeration or to lower temperatures for much shorter periods than are now required in federally inspected plants.

Obviously much more extensive study is needed on the possibilities of quick freezing, cooking and other methods of eliminating the *trichina* hazard. Once the condition has been largely eliminated from both American pork and American human beings, the conditions of control need not be quite so severe.

MORRIS FISHBEIN

1. Gould, S. E.: Incidence of trichinosis among county hospital patients in the Detroit area, based on 500 consecutive autopsies. Am. J. Clin. Path. (July) 1940.
2. ———: An effective method for the control of trichinosis in the United States. J.A.M.A. 129:1251-1254 (December 29) 1945.
3. ———: Diagnosis and treatment of trichinosis. Postgrad. Med. 5:257-269 (April) 1949.
4. ——— and Kaasa, Laurin J., with the technical assistance of Mildred L. Ransom: Low temperature treatment of pork: effect of certain low temperatures on viability of *trichina* larvae. Am. J. Hyg. 49:17-24 (January) 1949.

HOW OLD IS MAN?

Most recent views as to the age of man on this planet indicate that modern man goes back about 50,000 years. Recent biologic and anthropologic research seems to indicate that this brief interval rather than the million years usually estimated marks the entire existence of modern man since he evolved from a form of primitive ape. According to present day belief the brain which distinguishes man from other mammals was the last portion of man to develop. The anthropologists say that the structure of man's trunk and arms is roughly 10 million years old, the leg structure, which permits man to walk upright, is approximately one million years old and the human brain only 50,000 years old. It is nice to know these things but it is sad to think how little this modern brain has really learned as to avoidance of war and the practice of humanity in 50,000 years.

MORRIS FISHBEIN

Women in Medicine

Lady Doctor of the Blue Ridge

Drs. Eustace H. and Mary T. Martin Sloop

The directory of the American Medical Association states briefly that Dr. Mary T. Martin Sloop, Crossnore, Avery County, North Carolina, is "not in practice." Not strictly in active medical practice, true—nor, perhaps, is there a term inclusive enough for what she has done, in the last 40 years, to earn the title, "Grand Lady of the Blue Ridge." That is best told in the story of Crossnore, a remote mountain village of 300 people, which in 1911 had no school for its children and was a full day's trip by mule from the nearest railroad.

With the arrival in 1906 of Dr. Eustace H. Sloop and his wife, both from the University of Pennsylvania School of Medicine, Crossnore acquired both doctor and humanitarian, and a chain of events was set in motion which culminated, this year, in the designation of Dr. Mary T. Martin Sloop as the "American Mother of 1951."

It is a story remarkable in its steady progression toward great achievements and which extends far beyond a career of medical practice. One of Dr. Mary Sloop's first acts was to organize a sewing class for the mountain girls who had practically no educational or vocational opportunities, and whose most promising member was about to be married off while yet only 12 years old. By appeals to distant relatives and friends Dr. Sloop acquired enough castoff clothing to sell to eager mountain women, and thereby enough cash for necessary expenses so that the child might attend the nearest school instead.

It was not long before Dr. Sloop, confronted with more boys and girls who wanted schooling, proposed a small grammar school for Crossnore itself.

Today Crossnore School, fully accredited, provides education and vocational training for 1000 sons and daughters of the Blue Ridge. Here they are trained in arts and crafts, in carpentry, home economics, agriculture, and even in a two year business course.

In addition to bringing education to Crossnore, Dr. Sloop is credited with the results of her tireless efforts for better roads and school buses for outlying mountain districts. As for medicine, in recent years Dr. Sloop has left that to her husband and to her two children: Dr. Emma Sloop Fink and Dr. William Martin Sloop, a dentist, both of whom practice in Crossnore.

Last month, representatives of 40 United Nations countries gathered to honor Dr. Mary T. Martin Sloop for her distinguished achievements as physician, humanitarian and parent which exemplify the highest ideals of family and community service.

Correspondence Department

To the Editor:

THE GENERAL PRACTITIONERS' COAGULATION TIME TEST

The general practitioner, faced by the problem of a case of coronary thrombosis, although he knows perfectly what to do, wonders how he is going to do it. Having induced rest and relief of pain by morphine and atropine or papaverine and atropine and relieved tension with one of the other indicated drugs, he has time to face his next problem: what is the coagulation time of the blood?

He is far from a hospital or laboratory or no beds are available. He wishes he could make a test quickly himself. He knows of the Lee-White method, Quick's prothrombin test, which is out of his field, and the capillary glass tube method which is also out of his field because of lack of a gas burner or because all the fine tubes he has prepared for such a test are broken.

These difficulties led to the development of the General Practitioners' Coagulation Time Testing Method.

Every country soda fountain has easily obtainable wax paper straws. The ones I can buy in the small grocery store fit perfectly into a B.D. Tuberculin syringe barrel. They also fit into a standard hypodermic needle.

To test the coagulability, fit a tuberculin syringe barrel with a 20-gauge needle and sterilize. Insert a soda water straw snugly into the syringe and as a valve put another fine needle on the top of the straw.

Insert the sterile needle into the vein and allow the straw to fill to the top with blood. Withdraw and exchange the 20-gauge needle with an old blocked-up needle. Allow tube to stand for the number of minutes desired and with a sharp razor blade cut the top quarter-inch of straw three-quarters through. Every one or two minutes cut off another quarter- or half-inch until clotted blood is reached. Note the time. After using heparin or DICUMAROL® do not start cutting until previous clotting time has been reached.

E. V. Frederick, M.D.
Toronto, Ontario

NOTE ON LAENNEC

To the Editor:

The Medical Museum of the Armed Forces Institute of Pathology has an extensive collection of stethoscopes and hence the staff found your April issue of more than usual interest.

It was noted that in the sketch on Laennec the statement was made that the first stethoscope was a wooden cylinder. You may be interested in the following excerpt from Laennec's "A Treatise on the Diseases of the Chest and on Mediate Auscultation" as translated by John Forbes, and quoted by Cecilia Mettler in her "History of Medicine" (p. 303):

> "The first instrument which I used was a cylinder of paper, formed of three quires compactly rolled together, and kept in shape by paste."

He mentioned several materials with which he experimented and said:

> "In consequence of these various experiments I now employ a cylinder of wood, an inch and a half in diameter and a foot long, perforated longitudinally by a bore one-quarter inch wide, and hollowed out into a funnel-shape, to the depth of an inch and a half at one of its extremities."

We have found the illustrations of landmarks in medicine of particular interest for their artistry as well as their historical importance.

Ruell A. Sloan, M.D.
Curator, Medical Museum, Armed Forces Institute of Pathology, Washington, D. C.

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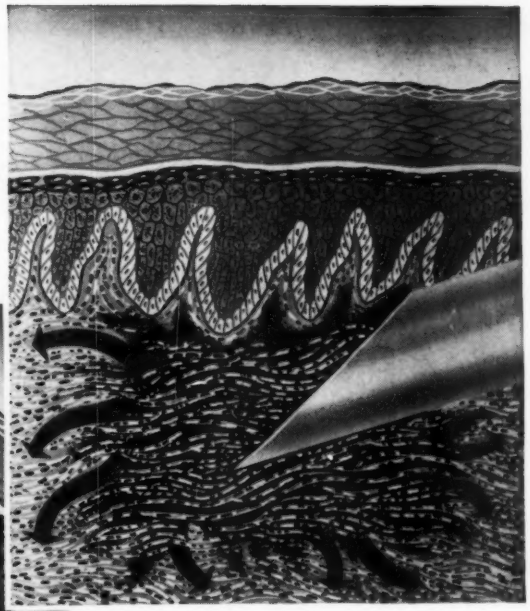

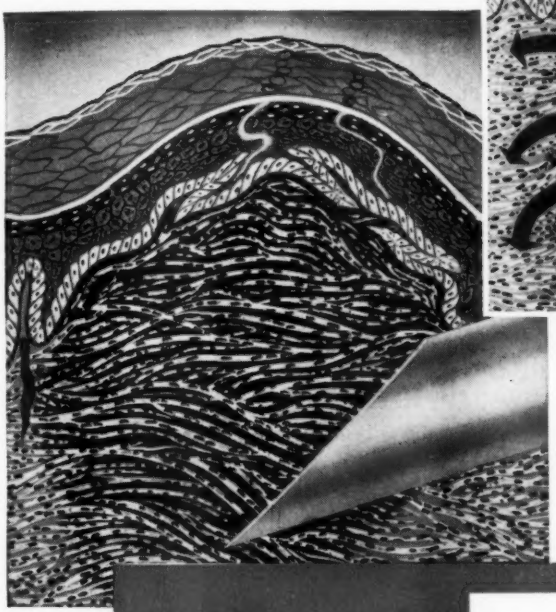

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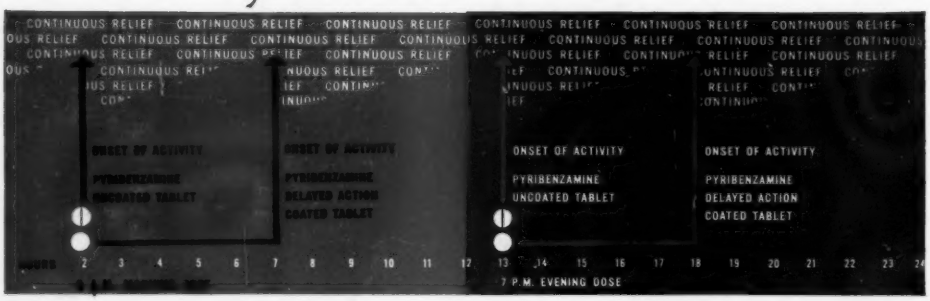
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